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ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 13 (O.S., Vol. XVIII) JUNE, 1940 NUMBER 12

CONTENTS

	Page
Medical Problems Encountered in Military Service. CHARLES C. HILLMAN	2205
Developments in Aviation Medicine. HARRY G. ARMSTRONG	2212
High Atmospheric Pressures; Physiological Effects of Increased and Decreased Pressure; Application of These Findings to Clinical Medicine. A. R. BEHNKE	2217
Epidemiology in the Army. JAMES STEVENS SIMMONS	2229
Results of the Use of Extract of the Intestinal Mucosa in the Treatment of Vasomotor Rhinitis. LOUIS E. PRICKMAN, HAROLD I. LILLIE, GRACE M. ROTH and RALPH G. FLEMING	2235
Clinical Desensitization to Wheat by Use of an Acetylcholine Derivative. EMMET F. PEARSON	2241
The Clinical Application of the Determination of Circulation Times. SAMUEL BAER	2246
Cardiac Hypertrophy; Forty-Two Hearts Weighing 750 Grams or More. G. F. STRONG and D. S. MUNROE	2253
Felty's Syndrome: Its Several Features, Including Tissue Changes, Compared with Other Forms of Rheumatoid Arthritis. A. C. CURTIS and H. M. POLLARD	2265
Subclinical Pulmonary Tuberculosis; A Presentation of Forty Cases. R. H. STIEHM	2285
Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, with Two Cases in Which the Same Agglutinogen Was Responsible. ALEXANDER S. WIENER and H. RAYMOND PETERS	2306
The Cardiac Output in Congestive Heart Failure and in Organic Heart Disease. HAROLD J. STEWART, NORMAN F. CRANE, ROBERT F. WATSON, CHARLES H. WHEELER and JOHN E. DEITRICK	2323
Case Reports:	
Hemochromatosis: Report of a Case in Which Tuberculous Peritonitis Was a Complication. CARL G. MORLOCK	2341
Chronic Leukopenia with Fatal Termination Due to Agranulocytic Angina; Case Report. ISRAEL KOPP	2347
Editorial	2355
Reviews	2359
College News Notes	2361
Minutes	2378
Index	2386

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $7.50, other countries.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 13 JUNE, 1940 NUMBER 12

MEDICAL PROBLEMS ENCOUNTERED IN MILITARY SERVICE*

By CHARLES C. HILLMAN, B.S., M.D., F.A.C.P., Colonel,
Medical Corps, U. S. Army

IN the world about us we now witness millions of people arrayed in bitter conflict against other millions, defenseless masses dying at the hands of ruthless aggressors, and commerce of neutrals as well as belligerents disrupted. We see peaceful peoples crushed by the humiliating demands of powerful neighbors and their cities leveled by the lightning thrusts of mechanized armies. We are confronted with unexpected and powerful coalitions, which are prompted solely on principles of expediency and greed. With these developments in current history we cannot but ponder over the future that fate holds in store for the American people and respond to the impulse for preparation against the possibility of an evil day that may befall us.

In contemplation of the duties which the Medical Department must assume as a component of the military forces of the United States, it has been deemed appropriate to review at this time some of the problems that are more professional in character which we as medical officers shall face in the event of war. To emphasize the fact that these are not purely academic considerations but are, on the contrary, very practical matters with which many of you may be intimately concerned, permit me to remind you that in case of a major mobilization it is estimated that we shall require from 15,000 to 40,000 commissioned officers in the Medical Department alone.

During the first phase of the conflict we shall be concerned with the mustering of manpower and the collection of thousands of young men from diverse localities into reception centers for equipment and training. The first effort of the newly mobilized medical officer will be directed to the physical examination of recruits and of registrants under the selective service act. No doubt all of you have considered the theoretical advantage of sending all the morons and the psychopaths promptly to the front, but un-

* Read at the Cleveland Meeting of the American College of Physicians, April 1, 1940.

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fortunately a superior army cannot be moulded from inferior individuals. The first call will be for the best of our young manhood, for individuals who can withstand the mental as well as the physical strains of war, and for men who have the intelligence to perform any of the multitudinous and hazardous tasks that may fall to the soldier in the field and during combat. Besides selecting men who may be expected to perform the most rigorous duties under conditions of adversity, the military surgeon has the equally important duty of excluding those of substandard mentality and physique. A weakling at the front is worse than useless; besides being of no value himself he will often require the time of an able soldier to give him care. Moreover, he quickly gravitates into the ranks of the compensable and comes out of the war with only a pension to his credit.

Since it is important for the individual as well as for his associates and for the pension rolls to exclude cases of pulmonary tuberculosis from military service, routine chest roentgenograms, or routine skin tests with roentgen-ray examination of positive reactors, will probably be employed to eliminate cases of tuberculosis that have not been detected by physical examination. Because of the special equipment that will be necessary to conduct rapid roentgen-ray surveys and the time required to interpret and report the findings, it will be practicable to conduct such general tuberculosis surveys only after registrants have been inducted and sent to reception centers. Those suffering from the disease will then have to be discharged on certificate of disability. It is anticipated that such discharges can be effected within periods sufficiently short that liability for the disease and resulting compensation claims will not devolve upon the Government.

In the reception centers to which newly inducted men will be sent following acceptance by medical examining boards you will be concerned largely with the prevention and treatment of the acute infectious diseases. Measles, meningitis, influenza, pneumonia, and other air-borne diseases will constitute your greatest problem. Since the epidemiological aspects of the situation will be discussed by a subsequent speaker, I shall attempt only to review briefly the importance of such diseases in unseasoned military personnel and some of the features of treatment.

The records of the World War show that in the American Army at home and abroad during the period April 1, 1917, to December 31, 1919, there were approximately 100,000 admissions for measles, 750,000 for influenza, and 75,000 for pneumonia. Your anxiety is not only over the individual case, but it is over the aggregate number of such cases for which you may have to care at times under war conditions. You will recall that some of these diseases swept through camps at times like hurricanes from the West Indies. It was my own experience during the fall of 1918 to witness the virtual transformation of a large training camp into an immense field hospital, with most of the well occupied in caring for the sick. In this camp of 42,000 men there were during one five-week period 8,984 admissions with 499 deaths, mostly from influenza and pneumonia. Because of overwork

and massive exposure, a large proportion of the medical and nursing staff was involved. Under such conditions one will readily understand that modern hospital care, with adequate nursing attention and ideal therapeutic management, is beyond reach. In this instance even the matter of embalming the dead became a serious problem. Hundreds of oxygen tents cannot be produced overnight. Even the typing of sputum and the administration of serum to all to whom it may advantageously be given will be difficult. It is under such extreme conditions that sulfapyridine and related remedies will reach their zenith of usefulness.

Military medicine is fortunate in the development of the sulfanilamide group of synthetic drugs. Their non-deteriorating qualities, small bulk, and wide application give them an unusual adaptation to military use. Another notable advance in military medicine has been accomplished in the lyophilization of therapeutic sera. The ability of such sera to maintain their potency over protracted periods of time has made it practicable, upon the threat of hostilities, to produce large supplies and to hold them in storage for emergencies.

It is interesting to compare the mortality rate of World War pneumonia with that of today. The average death rate for all pneumonias during the war period was approximately 24 per cent. In the American Army during the five-year period 1935 to 1939 it was 5.6 per cent. Since October 1, 1939, there has been a total of 1222 cases of pneumonia in the Army and in the Civilian Conservation Corps. Only 19 of these have terminated fatally, giving a mortality rate slightly under 1.6 per cent. Although it is realized that the pneumonia of 1918 was much more virulent than that of today, the marked reduction in mortality must be attributed in considerable part to improvements in the therapy of pneumonia. From this we may reasonably anticipate that the high mortality rate of 1918 will not attend future respiratory pandemics.

Before leaving the subject of respiratory diseases, it may not be inappropriate to recall the well known fact that early diagnosis, bed rest, and generous intake of warm nourishing liquids will be determining factors in carrying many through their influenzas and milder respiratory infections without secondary pneumonias; also, that careful sterilization of eating utensils and the use of cubicles improvised with sheets or shelter halves will greatly reduce complicating cross infections.

Another problem not so spectacular but none the less important will be that of venereal disease. It is reported that during the first World War there were 400,000 cases in the British forces in France. There were 340,000 reported cases in the American Army. To state it differently, one man in every eleven acquired syphilis, gonorrhea, or chancroidal infection.

Suppression of venereal disease is difficult because it is concerned with one of man's most primitive biological urges. The situation is ordinarily approached along three lines, viz., educational, prophylactic, and punitive. Educational activities include not only the enlisted grades but also officer

personnel, in order that both may be made cognizant of the serious nature of venereal infections. Line officers should be impressed early in their careers with the importance of these diseases as causes of high noneffective rates and permanent disabilities; also, with the fact that in any organization a high venereal rate usually reflects an underlying condition of administrative and disciplinary inefficiency. Realizing that educational measures are only partially effective, provision has been made for individual mechanical and chemical prophylaxis. The Medical Department maintains prophylactic stations at all military hospitals, and at other convenient points on posts and in nearby cities, for those who will avail themselves of cleansing measures and chemical prophylaxis following intercourse.

Punitive measures aside from loss of pay while away from duty because of venereal disease are less in vogue than formerly. While severe penalties, such as confinement and extended loss of pay, had a deterrent influence on promiscuous sexual exposure, such measures undoubtedly drove many infected individuals into the hands of charlatans and patent medicine vendors. Army Regulations at present permit trial by court martial only for those who having acquired venereal disease fail to report for treatment. It is believed that under these regulations early treatment will be the rule and many will be spared the devastating results of neglected gonorrheal and syphilitic infections.

An important element in the control of venereal disease is the coöperation of local police and health officials in extra-cantonment areas. With a frank yet diplomatic approach, much can be accomplished through these agencies. We are also assisted in the matter of extracantonment sanitation by the United States Public Health Service. During the World War, officers of this national agency rendered valuable aid as consultants on local health problems, in coördinating civilian police and health activities, and in crystallizing public sentiment toward supporting these organizations. Such assistance is now being rendered in coöperation with state and local authorities in southern training areas, and plans have been formulated whereby general assistance in extracantonment sanitation will be given by the Public Health Service in time of national emergency.

The problems that have been discussed up to this point have concerned activities largely in home territory. Aside from the number of men involved and the speed with which work must be accomplished, the medical situations are those which have their counterpart in civil practice. Moreover, plans for their accomplishment can be formulated quite accurately in times of peace. When one attempts to envisage the medical service in the zone of combat, it is vastly different. As there are new styles in the peaceful arts, so are there new fashions in the arts of war. Stable warfare has become more stabilized and mobile warfare more rapid than ever before in its movement. Whether we shall face a Maginot or a Siegfried line, or encounter a blitzkrieg as exemplified by the German advance on Poland, we cannot forecast. We may be sure, however, that wherever the conflict and

whatever its character, we shall find it necessary to adapt our medical activities more closely to the teamwork of the military machine in attaining its assigned objectives. The farther we advance toward the front the more certainly, and possibly the more painfully, will this be true. Our efforts will be directed largely on the hypothesis of rendering the most aid to the greatest number, always with success against the enemy the foremost consideration. Priority will necessarily be given to the movement of troops and artillery, and to the transportation of ammunition and other combat supplies. Medical apparatus will have to be curtailed accordingly. Only the most compact and essential equipment will be available. The practice of medicine and surgery will necessarily be adapted to the altered circumstances, and the success of the medical officer will depend greatly on his ability to learn a technic which will fit the occasion. In the American Expeditionary Force in France, many eminent surgeons failed to achieve success because of their inability to function with sufficient rapidity in times of stress and to adapt their methods to the limited equipment and restricted environment necessitated by the military situation.

In the theatre of operations the medical officer will continue to encounter infectious diseases and ordinary surgical problems, but in addition he will have to deal with battle casualties and possibly diseases peculiar to trench warfare. It should be borne in mind that your obligation to the wounded soldier will begin long before you will have had an opportunity to evaluate your personal reactions to shrapnel and machine gun fire. Your responsibility will begin with the training of Medical Department enlisted men in the rudiments of surgical technic, the application of dressings, the arrest of hemorrhage, the splinting of fractures, and the movement of the wounded without further injury or aggravation of their shock. It is only with great effort that the first-aid man can be trained to give the same meticulous care on the battlefield that he would give a similar case in the atmosphere of an operating room. Among all types of battle casualties, none will suffer more from unskilled first aid than will compound fractures of the long bones. Early splinting is to be considered a life-saving measure. On the other hand, the unnecessary movement of unsplinted fractures, with resulting secondary laceration of the soft tissues, hemorrhage, and increased shock, must be bitterly condemned.

War wounds, inflicted as they are through soiled clothing and equipment and unwashed skin, are contaminated wounds. Many will develop serious complicating infections. Ordinary pyogenic organisms, tetanus, and the gas-producing anaerobes will be the chief offenders. Early debridement and immobilization will be considered just as essential as they were in the closing days of the World War. Irrigation with Dakin's solution and other chlorine antiseptics will no doubt be used, but less extensively than formerly. In the treatment of gunshot wounds, as in the management of respiratory infections, great dependence will be placed on the sulfanilamide group of drugs, with the difference, however, that here they will be used for their

prophylactic as well as their curative value. The success that has attended primary closure of badly contaminated compound fractures after debridement and topical application of sulfanilamide crystals offers great encouragement for the similar treatment of war wounds. This method of treatment may also prove to be the ideal one for perfringens and other gas-producing infections. Antitoxin and roentgen therapy, now used extensively against these infections in civil practice, are not ideal therapeutic agents for use on the battlefield.

Against tetanus outstanding progress has been made since the World War. Discussion of the subject will be left, however, to an eminent worker in that field, who will address you within the hour.

The use of transfusions in the treatment of battle casualties is another matter that occupies the thought of military surgeons. The practicability of blood banks in civil practice is well established, but to supply blood for transfusion purposes in evacuation and surgical hospitals, and other medical installations near the front lines, is a very difficult undertaking. The great problems in military practice are those of preservation and transportation. Special thought is now being given to the matter of individual containers, portable refrigerators, and airplane transport, by means of which blood can be carried to the combat area in usable condition and administered in the minimum time. The practicability of utilizing blood from civilian sources will depend largely on the geographical location of the scene of hostilities. Any comprehensive plan for the use of whole blood in the combat zone will necessitate typing of all military personnel and recording the blood types on their respective identification tags.

The Geneva Protocol of 1925 prohibiting the use of asphyxiating and poisonous gases has apparently been observed by all belligerents in the present conflict. Whether its observance is prompted as a matter of honor or by fear of reprisals is immaterial, the possibility of chemical warfare must always be considered. In view of this possibility, research looking to the development of effective treatment against chemical agents is constantly in progress. In the treatment of pulmonary irritants it is believed that helium-oxygen mixtures will find valuable application.

Psychological emergencies, vitamin deficiencies, trench feet, trench fever, nephritis, stomatitis, pediculosis, and scabies may contribute to morbidity rates. Diseases endemic in the war zone will appear. In the tropical and subtropical states of the American continent malaria and other tropical diseases will be met. Notwithstanding the highly efficient sanitary organization that has been built up in the Canal Zone, malaria still constitutes a major medical problem. Yellow fever might again be a menace in time of war. In the unexpected event of hostilities in our western United States, Rocky Mountain spotted fever, tularemia, and relapsing fever would be encountered, and should we have to meet an enemy on our southern border typhus would be a disease with which we would have to reckon.

The present war in Europe has been called a war of miscalculation. The same may be said of every war. In the Spanish-American War typhoid fever proved to be the enemy which wrought the greatest havoc. In the World War influenza appeared as the hidden foe in our midst. In the future, new conditions of warfare, new weapons, and unusual diseases will throw unexpected responsibilities upon the Medical Department. The management of these new situations will tax our resources to the utmost and we shall undoubtedly find as we have found in the past that our greatest trouble will not be in a lack of medical knowledge but, instead, it will lie in the difficulty of applying common, well-known principles of medical practice to the abnormal demands of war.

DEVELOPMENTS IN AVIATION MEDICINE*

By HARRY G. ARMSTRONG, Capt. M. C., U. S. Army

A HIGHLY specialized field of medical science may normally develop in two directions, either by increasing the information available in its own particular field or by broadening its scope. As a result of the tremendous growth of the aviation industry in this country during the past few years aviation medicine has shown a marked development in both of these directions which has not only brought it into a position of prominence as a medical specialty but has made it a matter of interest and importance to the general medical profession as well.

Aviation medicine may be defined as that branch of medical science which has to do with the selection, maintenance, and treatment of those who fly. The first medical studies in aviation date back to 1783 when, for the first time, both experimental animals and human subjects were sent aloft in smoke filled balloons to determine the effect of flight on the living organism. Two years later, in 1785, the American physician, Dr. John Jefferies of Boston, flew over the English Channel from England to France during which he made notable observations of the aerial environment. Subsequent to the flight of Dr. Jefferies the advances in aviation medicine have been largely confined to three rather sharply defined periods of time.

The first of these occurred between 1875 and 1878 and was the result of the work of Paul Bert, the brilliant French physiologist. Bert became interested in the effect of flight after having read accounts of the strange symptoms suffered by Glaisher and Coxwell during a series of high altitude balloon ascents. The results of Bert's studies were published in 1878 in a volume of some 1100 pages and it is astounding the amount of original data which he presented at that time. Bert's work was of interest not only to aviation but to general medicine as well, for it included much of our fundamental knowledge concerning gaseous exchanges in the body, caisson disease, and other related phenomena.

The second period of great advance in aviation medicine came about directly as a result of World War I. At the end of the first year of that conflict some startling statistics were revealed. They showed that of every 100 pilots killed during that period 2 died as the result of enemy action, 8 from defective equipment, and 90 from defects in the pilots themselves. In some instances 50 per cent of the students developed neuroses in training before ever becoming graduate pilots. It was also noted that there were whole hospital wards full of trained fliers who were uninjured, suffering from no known malady, yet completely incapacitated for flying duty. These unusual circumstances immediately attracted the attention of the best medical minds

* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

in each of the combatant countries engaged in the war and a great amount of medical research was devoted to these problems during the remainder of that conflict. The tremendous advances made in aviation medicine during the World War I period will not be recounted here except to mention that it emerged in this country as a recognized specialty in military medicine and that a postgraduate school of training for flight surgeons was established as a permanent part of our Army medical education system.

The third and final period of great advance in aviation medicine began in 1926 and has persisted up to the present time. In 1926 the Bureau of Air Commerce of the Department of Commerce was established for the control of civil aviation and later supplanted by the Civil Aeronautics Authority. The medical section of these agencies grew rapidly as civil aviation expanded and at the present time requires the services of approximately 700 civil physicians. In addition most of the major airlines have established their own medical departments and hence created many openings for other qualified civil physicians since it is forbidden that one physician serve both the Authority and another civil agency. Thus since 1926, when aviation medicine was confined to the military services and non-existent in civil aviation the situation has changed to the extent that civil flight surgeons now outnumber those in the Army Air Corps by a ratio of approximately 4 to 1. Although the total number of qualified flight surgeons in this country is relatively small, there is a most unusual seriousness of purpose among them as evidenced by the fact that they have their own medical association, publish and read their own medical journal, and attend their own annual medical convention.

Thus far the development of aviation medicine has been outlined only in so far as it is practiced as a specialty. It remains to show its development as a field of interest and importance to other special fields of medicine and to medicine as a whole. In order to accomplish this it is but necessary to point out that civil flight surgeons are not officially responsible for the clinical care of pilots under their supervision nor do they have any direct contact with those who travel by air. Hence, all clinical matters concerning those who fly are a responsibility of the general medical profession. To the uninformed it may appear that there is an insignificant number of these individuals or that they present no usual problems. Neither of these assumptions is true as can be shown by the following considerations.

In this country today there are over 31,000 licensed airplane pilots and 15,000 more are now in the process of being trained. The licenses of these individuals, and in many instances their livelihood, depend on the proper maintenance of their mental and physical health under the supervision of the family physician. In aviation the term physical fitness has a special significance. Naturally health is included in its general meaning but is by no means synonymous with it. Perhaps this last statement can best be emphasized by pointing out that a candidate for an air transport pilot's rating

may be free from all acute disease processes, have no obvious gross physical defects, be capable of engaging in most other occupations, and yet have over 100 disqualifying defects for flying. While it is true that many of these so called defects have no great clinical significance they have been found important in aviation and must be taken into consideration in any program of medical care if that program is to be a success.

In addition to the clinical care of pilots the general medical profession is also responsible for all medical matters with reference to civil air passengers. Altogether last year in scheduled and unscheduled passenger operations over 3,000,000 passengers were carried aloft into an unnatural environment. This is not to imply that modern air transportation is dangerous to life for it is not. It does mean, however, that our people are becoming air minded and are being exposed to new unnatural conditions, however subtle, that may affect them adversely under certain circumstances. The coming magnitude of this problem is almost unpredictable. In a recent comprehensive survey the American Institute of Public Opinion found that 42 per cent of the population of this country expressed a desire to learn to fly. That per cent amounts to 50,400,000 people. By no means is it intimated that all of these people are actually going to learn to fly but some of them are and many more will fly as passengers. Among both of these groups there are many who will be in need of medical service and guidance.

What are the medical requirements for a private pilot's license, a commercial pilot's license, an airline pilot's license? What effect does flight have on damaged hearts, on pulmonary disorders and on gastrointestinal disturbances? Are common colds, middle ear infections, or infected sinuses contraindications to flight. Should infants and the aged travel by air? Is flying safe and if so, as compared to what? What is airsickness, aero-otitis media, aeroembolism and other diseases peculiar to flight and under what conditions do these diseases develop and why? These are the questions that are being asked of the general medical profession today and those who are intelligent enough to ask are entitled to receive an intelligent answer. Especially is this so in the case of invalids or those seriously ill patients being transported by air as emergencies to take advantage of unusual skill or equipment at some distant point. In these instances the question of air transportation is often vital.

I especially wish to refer to the eight or ten million young men and boys who sincerely want to take up aviation as a career of whom probably only 1 to 2 per cent can ever qualify. It has been our experience that most of these young men consult their family physicians before appearing for their official flying examinations to determine whether or not they are physically fit to fly or to institute remedial measures for any correctable defects which they may have. In the past this procedure, unless the candidate happened to be fully qualified for flying training, has usually led to a long chain of most unfortunate circumstances due to the average physician's complete lack

of understanding of the physical and mental requirements for aviation. As mentioned above good health and fitness for flying are not synonymous. As a consequence a good clinical examination is not necessarily a good aviation examination and the former is never adequate. Based on a clinical examination alone many a young man has been assured by his family physician of his physical excellence, has spent much time and money preparing for a career in aviation, and then failed his official examination for flying. This invariably leads to a recitation by the candidate of his examination by the family physician, the wasted time and money to which he has been subjected, and invariably an accusation of incompetence against the official examiner. The latter in defending his action can leave no other conclusion in the mind of the candidate but that it was the family physician who was at fault.

There is yet one final reason why the general medical profession should interest itself in aviation medicine and this pertains to considerations of national defense. All of the major conflicts since World War I have demonstrated the fact that the air arm is not only the first to be engaged but that it is likely to be the deciding factor in any struggle. This means that the air arm must be at full strength in men and materials at the beginning of hostilities and remain so until hostilities have ceased. While the difficulties of mass production of aircraft is generally known, few persons realize that the mass training of pilots is even a more difficult one. It must also be remembered that the initiation of pilot selection and training must await the organization and training of properly qualified medical personnel. If this vital function is to be properly performed, the necessary number of civil physicians must be selected, organized, and trained before an emergency exists. For this reason alone, if for no other, the general medical profession must familiarize itself with the fundamental principles of aviation medicine to the extent that is necessary for our national defense.

Means for accomplishing this are provided by the Army Medical Department through courses of instruction to medical reserve officers and medical officers of the National Guard at the Army Air Corps' School of Aviation Medicine at Randolph Field, Texas. Evidence that this course is popular with eligible officers and that our military problem in this respect is being met is indicated by the fact that over 300 officers have already graduated from this school and about 600 more are currently under instruction.

In civil life, on the other hand, the recent great expansion of the aviation industry has created a need which our medical schools have as yet made no organized attempt to meet. In this respect they have lagged behind most of the medical schools of Europe and especially those of Germany where, for the past two years, aviation medicine has been taught to every student as a regular part of his medical education. The growing need and the growing demand for such instruction in this country have, however, not been entirely without results. The first step in this direction has already been taken by

the George Washington University School of Medicine which presented a postgraduate course in aviation ophthalmology and aviation medicine in April of this year, and at least two undergraduate schools have recently introduced lectures in this subject to their junior and senior classes.

With this encouraging beginning it does not seem unreasonable to assume that all of our undergraduate medical schools will eventually provide their students with regular courses of instruction and that other postgraduate courses in aviation medicine will be presented as rapidly as conditions permit.

HIGH ATMOSPHERIC PRESSURES; PHYSIOLOGICAL EFFECTS OF INCREASED AND DECREASED PRESSURE; APPLICATION OF THESE FINDINGS TO CLINICAL MEDICINE *

By A. R. Behnke, Lieutenant, Medical Corps, U. S. N.

The present discussion concerns the effect of wide variations in atmospheric pressure on individuals whose usual environment has been completely altered by temporary existence in a pressure chamber, diving suit, or at high altitudes.

While these observations may be interesting primarily to workers in experimental medicine as general biological phenomena, certain physiological principles underlying the environment of the aviator and deep sea diver will be of value to physicians interested in inhalation therapy and in the utilization of pressure chambers for diagnostic and therapeutic purposes.

Primary Pressure Phenomena in Relation to the Paranasal Sinuses and the Ear. A consideration of pressure makes necessary the distinction between the manifestations of pressure per se, and the disturbances in gaseous equilibria in the body incident to pressure variations. Apart from disturbances in gaseous equilibria, pressure as an ecologic factor can be reduced to one-fifth of an atmosphere or increased to 15 atmospheres without demonstrable physiological effect provided that equalization of pressure takes place in the air spaces of the ear and sinuses. If, for example, the sinus and auditory tube passages are patent, the body can be subjected first to a sea water depth of 500 feet or a pressure of 240 pounds per square inch and then to an altitude of 38,000 feet equivalent to a pressure of 3 pounds per square inch without demonstrable injury.

If, on the other hand, the openings of air spaces in the ear and sinuses are occluded, then slight pressure variations in the range of 1 or 2 pounds (50 to 100 mm.) per square inch elicit painful response and induce congestion, edema, and hemorrhage in the affected tissues.

The manner in which pain is elicited may be surmised from the diagram in figure 1 which represents the body as a mass of protoplasm consisting of 70 per cent fluids and 15 per cent fat, and almost completely enveloping numerous cavities. If this body is subjected to increased pressure, every air pocket present from the smallest ethmoid cell to the air cells in the tip of the mastoid process receives air, provided that the ostia of these spaces are open. If under the same conditions the ostia are occluded, the pressure within the pneumatic space tends to remain constant while the increased

* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.
The contents of this paper are not to be construed as an official expression of the Navy Department.

pressure force acting on the body mass and circulating blood puts tension on the cells of the lining membrane and serves to dilate blood vessels in tissue surrounding the occluded space. With reference to the sinuses it is con-

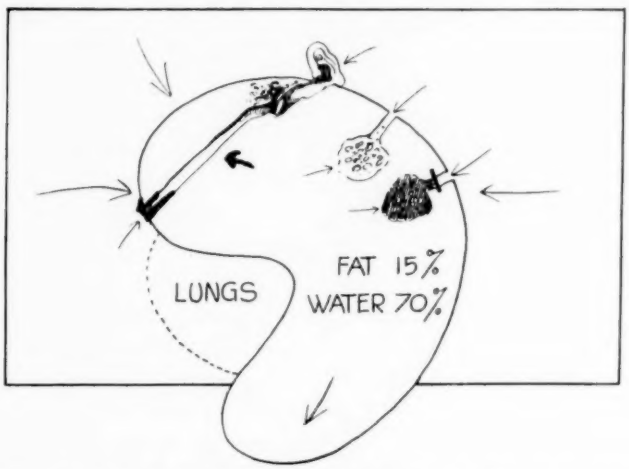

FIG. 1. Diagram to illustrate the effects of pressure on the body showing equalized pressure on the tympanic membrane and in a sinus space, and congestion and hemorrhage into a sinus space when the opening into the sinus is blocked preventing equalization of pressure.

ceivable that the congested and hemorrhagic epithelium and tunica propria tend to separate from the bony wall and to evaginate into the space of lower pressure. Pain located in and around the involved area is the concomitant symptom of the pressure force created by difference of pressure between the lining membrane and the adjacent air medium.

With reference to the ear, prior to the onset of pain as the differential pressure is increased, the blood vessels best observed within the tympanic membrane in the area of the short handle of the malleus, are seen to dilate presenting the appearance of a radiating network. Further increase in pressure ruptures vessels and elicits a painful response felt within the ear and over the mastoid area. The tympanic membrane is ruptured in the range of pressure between 5 and 10 pounds (250 to 500 mm.) per square inch.

The most important factor preventing accommodation to increased pressure and one to which individuals are predisposed, is acute or chronic upper respiratory tract infection.

The prevalence, for example, of complete or partial blockage of one or both auditory tubes is shown by the fact that out of two thousand qualified submarine personnel, 10 to 15 per cent were unable to tolerate pressure in excess of 5 or more pounds per square inch. Similar tests indicate that among the civilian population this percentage may run as high as fifty.

The Pressure Chamber as a Therapeutic Appliance. Utilization of pressure chambers in the submarine service makes possible a convenient method for diagnosis of congestion around the ostia and within the auditory tube

and sinus meatus. It serves also as a rapid, presumptive test of physical fitness, since individuals able to accommodate to pressure increases at the rate of 30 pounds per minute are usually free from infection of the nasopharynx. Deviations from this standard rate of pressure accommodation are usually in proportion to the severity of the disease process.

As an appliance for bringing about ventilation and drainage of ear, sinus, and pulmonary air spaces, the utilization of a pressure chamber is physiologically sound, but the therapeutic value may be limited by the consideration that immunologic factors appear to be of prime importance in the healing of pulmonary and sinus membranes rather than the mechanical factor of drainage.

In civilian life small pressure chambers might be utilized by the otolaryngologist and bronchoscopist for diagnostic and therapeutic purposes. Undoubtedly severe trauma has been inflicted on membranes by the use of suction apparatus. Suction applied to occluded sinuses in which the pressure is already decreased as a result of partial oxygen absorption, may induce drainage only at the expense of the epithelial membrane which becomes congested and hemorrhagic.

The application of positive pressure up to 10 pounds (500 mm.) per square inch in a chamber followed by subsequent release of pressure provides effective ventilation and drainage with minimum trauma.

Therapeutic appliances operating on the principle of alternate pressure fluctuations are the Drinker respirator, and various types of equipment designed to increase circulation in the extremities. It is not clear, however, that blood flow is increased in an extremity subjected to negative and positive pressure. It appears more likely that the term applied by Herrmann, "passive vascular exercise," describes the functional adjustment incident to compression and decompression, consisting essentially of a proportionately greater distribution of blood to the cutaneous area without significantly increasing blood flow to the extremity as a whole.

Effect Of Pressure Variations on Hearing. The problem of impairment of hearing as a result of pressure variations has received considerable attention in aviation medicine. We have observed that pressure trauma to the tympanic membrane, beginning with congestion and terminating in hemorrhage and perforation of the drum, is quickly repaired without permanent loss in auditory acuity.

Audiograms obtained on 19 deep sea divers subjected to pressure trauma over a period from 5 to 15 years show some loss in auditory acuity in the range of 4096 double vibrations. This impairment, however, does not affect hearing for spoken voice, and may reasonably be attributed to a degeneration of nerve elements in the cochlea, brought about by noise,[1] or incident to age.

Part II. Effects of Pressure in Relation to Disturbances in Gaseous Equilibria in the Body

The more important physiological phenomena incident to barometric pressure manipulation are related to the property possessed by gases of diffusing into the body when the atmospheric pressure is increased, and to the difficulty in their removal when the pressure is subsequently lowered.

Nitrogen Absorption and Elimination Curve. The manner in which atmospheric nitrogen diffuses into or from the body by means of the circulating blood when the air pressure fluctuates, is indicated by the graph in figure 2. Since the body solvents for nitrogen are fluid and lipid constit-

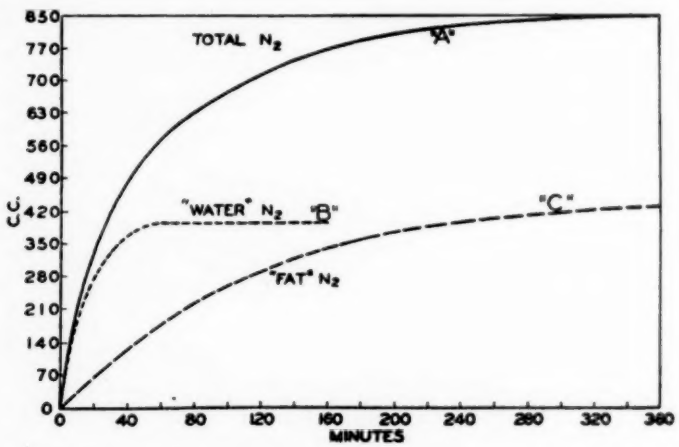

Fig. 2. Solid line shows nitrogen elimination from a young, lean man weighing about 60 kilograms. The nitrogen in the body is soluble in fat and fluids. The elimination or absorption of this nitrogen with changes in barometric pressure is represented by the hypothetical, broken-line curves on the graph. (Reproduced from the Am. Jr. Physiol., 1935, cxiv, 138.)

uents of tissues, and hemoglobin, hypothetical curves "B" and "C" of figure 2 indicate probable rates of nitrogen absorption or elimination from these materials. The quantity of nitrogen diffusing into the body is therefore a function of body weight, and since the fat-water solubility ratio of nitrogen is about 5 to 1, the volume of nitrogen absorbed reflects the fat content.

We [2] have made approximations of the fat content of the dog's body by measuring the volume of nitrogen eliminated during the respiration of oxygen. A knowledge of the solubility coefficients of nitrogen in water and fat and the determination or estimation of the water content allow the computation of the amount of body fat.

Helium has a fat-water solubility ratio of 1.7 to 1 or approximately one-third the rate for nitrogen.[3] While the helium absorption curve, figure 3, is similar in shape to the curve for nitrogen, the helium content of the body

is about 45 per cent of the nitrogen content, and the elimination rate of helium is about twice the rate for nitrogen.

Exercise increases the rate of gas elimination, but the value of exercise is chiefly during the first 30 minutes, when the inert gas is diffusing from body

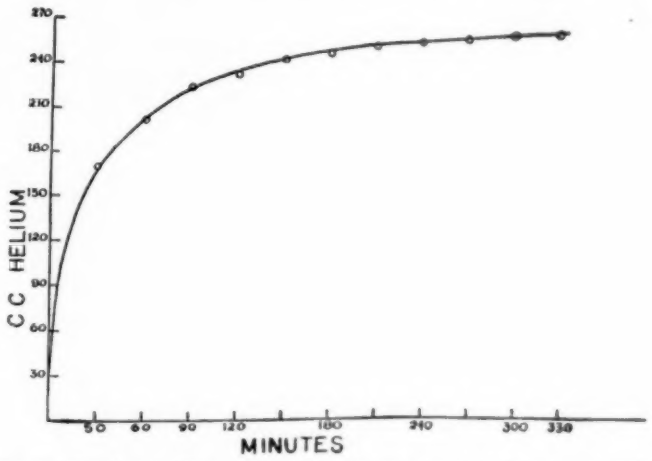

FIG. 3. Curve showing helium elimination from a young, lean man weighing 74 kilograms. Subject was previously exposed three and one-half hours to an atmosphere containing about 75 per cent helium. (Reproduced from the U. S. Nav. Med. Bull., 1938, xxxvi, 542.

fluids. Exercise does not greatly influence the elimination of inert gas from the fat depots of the body.

Circulatory Efficiency in Relation to Rate of Gas Elimination from Tissues. The rate of nitrogen removal is a function of cardiac output which in turn is related to metabolic mass or surface area. Small mammalian species with a comparatively large surface area in proportion to body weight eliminate excess nitrogen so rapidly from their tissues that it is difficult to produce air embolism in these animals following exposure to high pressures. For example, the rate of nitrogen transport in the dog is about double that in man.

Taking these facts into consideration it has been possible to develop an exacting test of circulatory efficiency by introducing an excess quantity of nitrogen into the body tissues during exposure in a high pressure atmosphere and then rapidly decreasing the pressure to normal.

The elimination of the excess gas from the tissues without the development of extensive air embolism upon return to normal pressure depends primarily upon effective blood flow through the tissues. Both cardiac output in relation to body weight and the adequacy of collateral circulation are the important factors preventing accumulation of air emboli in sufficient number to elicit pain in the affected parts.

Physiological Reactions Associated with the Absorption of Nitrogen. Beginning at an absolute pressure of about 4 atmospheres, nitrogen acts as a

narcotic to depress neuromuscular activity. At a pressure in excess of 10 atmospheres, consciousness may be lost. This remarkable property of nitrogen is consistent with the Myer-Overton hypothesis relating narcotic action to solubility in lipid substances of the central nervous system. Whether or not there is interference with carbon dioxide elimination in the denser atmosphere has not been determined.

The substitution of helium for nitrogen abolishes the narcotic effects of pressure, and an individual breathing a helium-oxygen mixture feels nearly as well at a pressure of 16 atmospheres as he does breathing air at normal barometric pressure.

It may be of interest to record that argon, like helium, possesses complete chemical inertness but unlike helium, it brings about a neuromuscular impairment and psychic depression somewhat greater in degree than does nitrogen.

These physiological studies of elementary gases apparently reveal an avenue of approach to the fundamental nature of anesthetic activity. Apart from the selective solubility of the heavier gases in lipids compared with water, the crucial consideration centers around the question of interference with oxidative systems in cells by a blanketing effect tending to limit oxygen diffusion through the cellular membrane.

Reactions Associated with High Pressures of Oxygen. Of the gases diffusing into the body under increased pressure, oxygen is of greatest importance. In the Navy, an important advance in the field of diving is the employment of oxygen for the prevention and treatment of compressed-air illness. During rescue and salvage operations connected with the U.S.S. Squalus disaster, the administration of oxygen constituted a life-saving measure. Oxygen, however, is toxic at higher pressures, and in the course of investigations to ascertain the value of oxygen, tolerance studies received first consideration.

At sea-level pressure, the period of time that pure oxygen can be safely breathed is a matter of controversy. Although the tolerance of the anoxemic patient may be greater than that of a healthy individual, we find that healthy men between the ages of 20 and 40 are able to breathe 99 per cent oxygen for periods not in excess of seven hours. During this tolerance period, slowing of the pulse rate and pallor are observed. If it is inhaled for a period in excess of six or seven hours, there may be a break in compensation characterized by increased depth of breathing (figure 4) suggestive of accumulation of carbon dioxide in tissues. When this break in compensation takes place the inhibitory action of oxygen on the chemoreceptors of the carotid body is replaced by a reaction typical of the stimulating effect of carbon dioxide on the respiratory center, a phenomenon of which the individual himself may not be aware.

Toxic symptoms associated with oxygen breathing and suggesting a break in compensation are flushing of the face and nausea. By reason of its recurrence when oxygen is breathed at pressures of two and one-half to

three atmospheres, nausea is regarded by us as a pathognomonic symptom of oxygen toxicity.

Pure oxygen moreover is a pulmonary irritant and numerous investigators have described the edema and pneumonia incident to oxygen inhalation in tests employing rabbits, dogs, and rats.

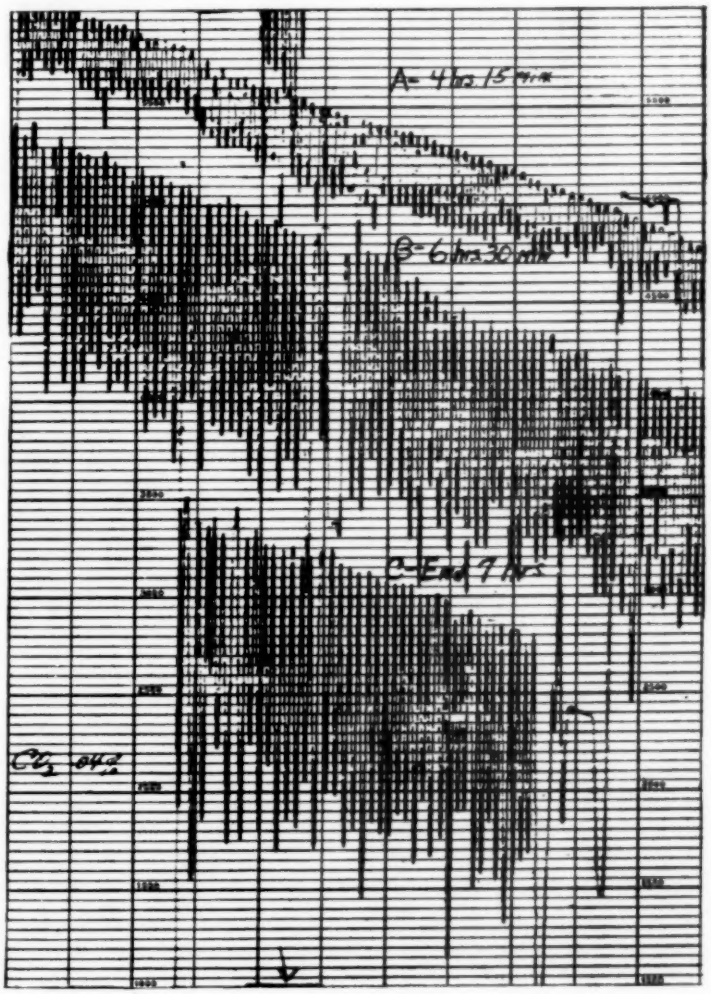

FIG. 4. (*A*) Amplitude of respiratory excursion after 4 hours of pure oxygen inhalation at sea level barometric pressure. (*B*) Amplitude of respiratory excursion 6 and one-half hours from the start of oxygen breathing.

I desire to stress the fact that our tests utilizing 99 per cent oxygen at sea level pressure are frequently terminated at the end of six hours by the complaint of substernal soreness aggravated by deep inspiration or smoking. Although auscultatory and roentgenologic examination reveal no positive findings, the symptom of substernal distress points to the irri-

tant property of pure oxygen and indicates pulmonary congestion or cardiac vasomotor spasm.

The cause of the toxic action of oxygen is not known. There is evidence that the accumulation of carbon dioxide in tissues as a result of disturbed transport incident to oxygen inhalation plays some rôle in the etiology of oxygen poisoning. In what may be termed the compensatory period, symptoms are indicative of stimulation of the sympathetic division of the autonomic nervous system. When a break in compensation occurs, the symptoms of flushing of the face and nausea in man, and a fall in blood pressure in anesthetized dogs suggest the action of a parasympathicomimetic drug. The action of a histamine-like substance,[6] or choline derivative, explains many of the toxic symptoms associated with oxygen inhalation particularly at the higher pressures.

With regard to oxygen inhalation at a pressure of 3 atmospheres [4] the oxygen taken up by the blood in physical solution is sufficient to meet the tissue requirements so that oxyhemoglobin is not reduced. At this pressure oxygen can be tolerated for a period of three hours.

At a pressure of 4 atmospheres [5] severe convulsive seizures are observed after about 45 minutes of oxygen inhalation. These seizures are similar to epileptic convulsions except for greater intensity and longer duration. Recovery is apparently complete when air is again breathed. In dogs prolonged oxygen breathing leads to a gradual paralysis of respiration.

In these oxygen studies the importance of diffusion as a property of gases is continually manifest. For example, the oxygen content of arterial blood drawn from a peripheral vessel is lower than that of blood equilibrated with the same oxygen pressure existing in the pulmonary air due in part to the diffusion of oxygen into vascular endothelium and adjacent tissue. If Exner's law of diffusion of gases through liquids is applicable to the diffusion of gases in the body, then the velocity of diffusion is proportional to the solubility coefficient and inversely proportional to the square root of the density of the gas. Campbell [7] has shown that the inhalation of pure oxygen at a pressure of one atmosphere raises the pressure of oxygen in certain tissues about 30 mm.

If the oxygen pressure is increased to 4 atmospheres, the quantity of oxygen going into physical solution in the tissues is strikingly apparent. During a period of oxygen inhalation for 17 minutes an apparent increase in oxygen consumption of 159 c.c. per minute or a 55 per cent increase over a control period was observed. This increase in oxygen uptake is explained on the basis of oxygen going into solution in the tissues; approximately 2.3 volumes per cent dissolve in fluids, and 11.2 volumes per cent dissolve in fat for every 760 mm. pressure at a temperature of 38 degrees centigrade.

Clinically some of these findings are of importance. Pure oxygen because of its toxic properties may be regarded as an inhalation drug tolerated by healthy men for a period of six hours and associated with symptoms suggesting stimulation of the autonomic nervous system. It should be realized

of course, that lowering the oxygen percentage greatly extends tolerance time so that 60 per cent oxygen at sea level pressure can be breathed for periods of months.

The diffusion of oxygen into tissues emphasizes its specific value in the treatment of such conditions as acute coronary thrombosis, lessening pain and limiting cardiac damage.[8] The neglect shown in the utilization of oxygen in acute coronary heart disease, especially when an individual appears to be in shock from anoxia, reflects undoubtedly a lack of familiarity with inhalation therapy as an integral part of therapeutic procedure, or perhaps a lack of appreciation of the clinical pathology underlying this condition.

In such conditions as acute pulmonary edema and carbon monoxide poisoning where advantage needs to be taken of oxygen in solution, special equipment would be necessary to create high pressure atmospheres.

At 4 atmospheres' pressure, in view of questionable methods of inducing shock therapy in mental patients, as for example, asphyxiation with nitrogen, experimental oxygen inhalation to induce seizures appears to be justified.

Part III. Observations Relating to Nitrogen Bubble Formation Following Exposure to High Barometric Pressures

Of great interest and worthy of more extensive study are the responses brought about by the presence of gas bubbles in the blood stream. In no other way perhaps, are weaknesses in the circulatory system made more apparent than by the presence of small air bubbles.

In the Navy one of our problems is to protect deep-sea divers from developing extensive air embolism following too rapid decompression from high pressure atmospheres. Aviators in rapid ascents to high altitudes are also exposed to the hazard of air embolism.

Although bubbles evacuated in the blood of aviators during rapid ascents to high altitudes contain high percentages of carbon dioxide, yet it is the high partial pressure of nitrogen in the body in relation to the external pressure that initiates bubble formation giving rise to the depressive fatigue, and at times pain incident to high altitude flights. Insofar as the problem of bubble formation is concerned, an ascent by an aviator from sea-level (1 atmosphere) to an altitude of 33,800 feet (0.25 atm.) is equivalent to an ascent by a diver from a depth of 100 feet (4 atmospheres) to the surface (1 atm.).

Bubble formation in divers is a common occurrence following decompression. In small quantities bubbles produce nothing more than pruritus usually more intense in the lobes of the ear and over the chest and abdomen. If the skin is chilled, the attendant vasoconstriction and slowed circulation enhance the liberation of gas in bubble form. Frequently a transient abdominal rash is observed which may closely resemble a macular eruption of secondary syphilis.

I believe that these symptoms are indicative of intravascular rather than

cellular or intercellular bubble formation. The disappearance of the skin rash, for example, is frequently too rapid to be accounted for by the presence of extravascular bubbles. In dogs rapidly decompressed from high pressures the veins may be filled with gas bubbles, while the lymphatic vessels are free from bubbles. Further, the remarkable amelioration of symptoms brought about by recompression without residual damage strongly supports circulatory impairment as the prime cause of symptoms rather than pressure on cells exerted by free gas.

Bubbles when first formed circulate through the whole vascular system and accumulate later in the large veins. Both pulmonary and peripheral capillary beds serve to trap the free gas. In the pulmonary vascular bed gas emboli increase resistance to the contractions of the right ventricle. Pulmonary gas emboli cause substernal and precordial distress aggravated by deep inspiration which elicits the cough reflex.

The substernal distress appearing several hours after exposure in compressed air is frequently accompanied by an exhausting fatigue which suggests an impaired venous return of blood to the right side of the heart. The wide dissemination of gas emboli in the pulmonary bed increases substernal distress and brings about asphyxia by interference with alveolar aeration and oxygenation of blood. The descriptive term, "chokes," has been applied by caisson workers to the symptoms induced by pulmonary embolism.

Since impairment of blood flow gives rise to the symptoms of compressed-air illness, it may be logically inferred that those parts of the body affected first by gas emboli would be areas of deficient circulation as the region of the joints and certain areas of the spinal cord. This inference is verified by our clinical findings. The region of the knee is most frequently involved and the sensation of pain is felt in the head of the tibia or the distal end of the femur. The term "bends" has been applied by divers and caisson workers to pains in the extremities. A feeling of stiffness may precede the onset of pain. In the extremities areas of previous injury as the site of an old fracture may be the first to give rise to pain. While pain around the joints usually follows long exposure in compressed air suggesting the liberation of free nitrogen gas in vessels within bone marrow, the symptom also appears after short exposures indicating susceptibility of joints or the distal ends of long bones to deprivation of blood supply by gas emboli disseminated from the general circulation.

The area in the spinal cord most frequently affected by embolic ischemia is the lower dorsal and upper lumbar portions giving rise to weakness of the lower extremities, spastic paraplegia, and genito-urinary impairment. Typical of the sudden onset of symptoms referable to the spinal cord is the history of a diver who remained in excellent condition for a period of four hours following a long exposure under pressure equivalent to a depth of 60 feet. No sooner had a notation been made in his record to the effect that he appeared to be in excellent health, than it was reported that his legs were

numb and unable to support his weight. No other symptoms were present and immediate and prolonged recompression brought about complete recovery.

Clinical conditions manifesting symptoms similar to those associated with the presence of air emboli in the spinal cord are tabes dorsalis, and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries. Reichert et al.[12] described the condition of four patients who exhibited weakness of the thighs on exertion, not accompanied by pain and associated with normal pulsation of the femoral arteries. These patients showed, however, extensive calcification of the terminal aorta. Reichert confirmed his observations by producing a similar syndrome in dogs following ligation of the lumbar segmental arteries.

The effect of interference with the blood supply to tissues by intravascular bubble formation in young, healthy, vigorous men simulates the symptoms associated with the aged or with individuals afflicted with arteriosclerosis or syphilitic arterial disease.

Fortunately, incipient lesions incident to ischemia induced by gas emboli undergo rapid resolution if blood flow is promptly restored by the application of adequate recompression.

In brief, we desire to stress the fact that air embolism following decompression from high pressure atmospheres or decompression from normal atmospheric pressure to sub-stratosphere levels, affects most frequently areas prone to injury by reason of poor blood supply. The cerebrum, cerebellum, and pons usually escape serious injury even when the emboli are widely distributed; i.e., paralysis of cerebral origin is, for example, rare. The viscera also do not show residual damage undoubtedly because they possess excellent collateral circulation.

Summary

1. The physiological effects of increased pressure up to 16 atmospheres or pressure decreased to one-fifth atmosphere fall into two groups, (*a*) effects of pressure per se, and (*b*) phenomena associated with disturbances in gaseous equilibria.

2. The primary pressure effects are observed if auditory tube and sinus openings are not patent. Obstruction creates a differential pressure between tissues and the adjacent air spaces. Pain is elicited as a diagnostic symptom and is associated with congestion and hemorrhage of membranes lining the occluded spaces.

3. Of the gases absorbed under pressure, (*a*) atmospheric nitrogen exerts a narcotic effect, minimized or abolished by the substitution of helium; (*b*) pure oxygen at atmospheric pressure elicits symptoms of bronchial irritation or vasomotor spasm if breathed for six or seven hours, and at a pressure of four atmospheres induces convulsive seizures followed by apparently complete recovery.

4. Observations are presented describing the effects of air emboli formed following decompression from high pressure atmospheres, the emboli affecting those parts of the body having poor circulation.

5. The clinical significance of the data is discussed particularly with reference to the use of a pressure chamber for diagnostic purposes, and to the value of certain aspects of oxygen therapy.

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EPIDEMIOLOGY IN THE ARMY *

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I. Introduction

The task of safeguarding the health of the American soldier, especially during war, is a responsibility of the entire medical profession of the United States. It has always been the policy of our peace-loving nation to maintain only a small regular army, capable of rapid expansion during emergencies by the addition of civilian soldiers. Likewise, the medical care afforded the troops during each of our major wars has been provided largely by the mobilized doctors of the country; and the quality of this service has reflected the status of medical development at the time.

With this responsibility in mind, the present chaotic international situation is sufficient to cause the physicians of America to give serious consideration to the medical problems which will arise should the nation again be forced to mobilize. Undoubtedly, one of the most important of these problems will be the prevention of communicable diseases, especially the infections, which frequently occur among troops in epidemic form.

In this talk we are concerned primarily with military epidemiology in its broader sense. After indicating some of the characteristics of the soldier and the dangers to which he may be exposed during peace, mobilization, and war, we will consider certain groups of diseases against which he can be protected, and others for which effective control methods are still urgently needed.

II. Physical Characteristics of the American Soldier

At the time of his enlistment the American soldier is a healthy young man between 18 and 35 years of age. Because of the physical standards required for his selection, he is relatively free from disabling anatomical defects and disease. During the World War, when more than 4 million men were mobilized, about 92 per cent were white, and the others were either colored or natives of our colonial possessions. As the Army is recruited from all sections of the country and from every social group, its personnel is made up of a mixture of all the races and classes included in our heterogeneous population. The magnitude of the task of protecting the health of these individuals can be visualized by reviewing some of the hazards peculiar to military life and evaluating the medical facilities now available for meeting them.

* Read at the Cleveland meeting of the American College of Physicians, April 1, 1940.

III. The Hazards of Military Life

These hazards may be conveniently separated into three categories, namely: (1) those incident to peacetime service in the Regular Army; (2) those which arise during mobilization, and (3) those associated with actual warfare.

(1) *Peacetime Service in the Regular Army.* The peacetime life of the Regular Army soldier probably is as safe, if not safer, than that of his brother in civil life. After being carefully selected, he is housed in modern barracks, fed a balanced diet of wholesome food, and forced to take adequate supervised physical exercise. He is trained in personal hygiene and required to carry out its principles. Finally, his health is constantly guarded by medical officers, and in case of illness or accident he immediately receives treatment in a modern Army hospital.

During 1938, when there were 182,000 men in the Army, the annual rate per 1000 for admissions to sick report was only 542, and the death rate was 3.2. These low rates indicate the satisfactory health conditions which now exist in the Regular Army.

(2) *The Hazards of Mobilization.* When mobilization occurs every effort is made to expand and continue the existing medical facilities. However, the rapid accumulation of recruits from all parts of the country and their concentration in temporary camps introduce new conditions which favor the development of such diseases as are transmitted through crowding and intimate contact among individuals. These unseasoned young men, possessing various degrees of susceptibility to infection, bring with them and introduce into the newly congregated groups an infinite assortment of the pathogenic organisms indigenous to their home communities. Such ideal conditions for herd infection have frequently resulted in epidemics of the diseases which are transmitted through the exchange of respiratory secretions. Naturally, the prevention of such outbreaks is a matter of great military importance.

(3) *The Hazards of Actual Warfare.* During actual warfare the soldier is not only faced with the danger of injury and death due to battle, but he continues to be exposed to infectious diseases, some of which may attack with such epidemic force as to jeopardize the attainment of military objectives. As the nature and severity of these infections depend on many complex factors, there has been considerable variation in the epidemics associated with our different wars. Yet, considered as a whole, disease has always been a more important factor than injury in the production of war casualties.

IV. Proportion of Casualties Produced by Disease and by Battle Injuries

Beginning with the American Revolution there has been a progressive improvement in the medical care afforded the sick and wounded of the

United States Army. However, in each of our wars epidemics have occurred, and the morbidity and mortality rates for disease have been higher than those attributed to battle. In the Mexican War (1846–8), for example, the disease deaths were seven times as numerous as those due to wounds. During the Civil War there were about 6 million admissions for disease, and the reported causes of death were: "unknown," 24,000; "battle injuries," 94,000; and "disease," 186,000. This result is not surprising, for at that time few of the microscopic agents of disease had been discovered and the microbiological sciences were unknown.

In 1898, when the United States engaged in its brief war with Spain, both bacteriology and protozoölogy were developing rapidly. The microorganisms responsible for a number of specific diseases had been discovered, and during that year Shiga incriminated the dysentery bacillus. However, the epidemiology of many infections was still imperfectly understood, and therefore military hygiene and sanitation were neither well developed nor generally appreciated. Again the infections, especially typhoid, caused a large proportion of the casualties, and for every man killed in battle seven died of disease.

Two decades later our Army entered the World War better prepared to meet the challenge of certain of the infectious diseases. Between April 1917 and December 1919 about 4 million men were mobilized—a larger army than had participated in any previous war in the history of man. In this enormous force the casualty rates for total diseases were considerably lower than in previous wars, there being 50,000 deaths due to battle and 58,000 attributed to disease. However, the respiratory infections were prevalent, and influenza appeared in virulent epidemic form.

Thus past experience shows that the activities of a military force may be seriously hampered by any one of a variety of diseases, and therefore it is difficult to predict the specific problems that may arise during a future emergency.

V. The Diseases of Mobilization and War

In making plans for the future one must consider all the important diseases that might interfere with the efficiency of troops during either mobilization or war. Naturally, the soldier is subject to most of the infirmities of mankind, but because of his age and the manner of his selection, he is less susceptible to the so-called endogenous diseases than to those which are exogenous in origin. The latter group includes various conditions associated with inanimate agents as, for example, the vitamin deficiencies, which have been eliminated during the present century by the application of our modern knowledge of nutrition and mess management. Of much greater significance are the specific diseases caused by living agents, many of which have ravaged the armies of man since the dawn of history. The scope of our future problems in military epidemiology may be visualized by briefly con-

sidering certain of these infections grouped loosely according to the methods of their transmission.

(1) *Wound Infections.* Since the time of Paré, when the wounded received little or no attention except that afforded by their comrades or female camp followers, there has been a progressive improvement in the treatment of wounds. The development of modern antiseptic surgery has resulted in a spectacular decrease in the morbidity and mortality formerly reported for wound infections. Nevertheless, such infections will continue to occur, and certain types, particularly those due to pyogenic organisms and the *Clostridia,* will always constitute a military hazard.

At present there is reason to hope that the pyogenic infections may be further reduced by the prophylactic use of sulfanilamide or some other chemotherapeutic agent; and that the use of tetanus toxoid for active immunization may eliminate certain difficulties inherent in the present method of prophylaxis. More satisfactory procedures are still required for the prevention of gas gangrene and other anaerobic infections of wounds.

(2) *Gastrointestinal Infections.* The gastrointestinal diseases, transmitted through the ingestion of contaminated food or drink, were long considered of primary military importance. During past wars many fine armies were crippled or destroyed by typhoid, the paratyphoids, dysenteries, and cholera. The evolution of methods for providing troops with safe food and water caused a material decrease in the enteric diseases, and Russell's development of an effective vaccine has practically eliminated typhoid from the U. S. Army.

For example, the diarrheal infections, which caused one-fourth of the disease casualties of the Civil War, were relatively unimportant during the World War, the admissions being only 22 per 1000 and deaths 0.07.

As to typhoid, Vedder stated that: " In 1898, during the Spanish American War the typhoid admission rate was 141 per 1000 and the death rate was 14. If this experience had been repeated during the World War, there would have been 560,000 cases and 56,000 deaths." In fact, during the latter war typhoid caused only 1529 primary admissions. (The admission rate was 0.37 and the death rate 0.05 per 1000.)

(3) *Venereal Infections.* Increased prevalence of the venereal diseases has long been associated with periods of military activity. This has been due in part to the fact that young men, whether congregated in barracks or elsewhere, fail to qualify biologically as " plaster saints," and in part to the mass hysteria with which war usually afflicts both men and women.

These diseases are of considerable military importance because of the disability which they cause and the time lost during treatment. Since the American Revolution, the Army has employed various methods in the attempt to reduce their incidence. These have included: loss of pay during hospitalization, trial by court-martial for misconduct, and the compulsory use of prophylactic measures. During the World War the admission rate

for venereal infections was almost 87 per 1000, or one-tenth of the total disease admissions; and they ranked second only to influenza as a cause of lost time. The prophylactic measures now in use are believed to be of definite value, but there is need for improvement.

(4) *Respiratory Infections.* The most important diseases encountered during the last war were those transmitted by personal contact and through the inhalation of infected droplets into the respiratory tract. Some of these, including influenza, the common cold, the pneumonias, diphtheria, scarlet fever, measles, mumps, and meningitis, occurred in epidemic form.

Three of the respiratory tract diseases, namely, influenza, bronchitis, and pneumonia, were responsible for over a million admissions to hospital and 44,000 deaths. This represented one-third of the total admissions for disease and 80 per cent of the disease deaths. Influenza alone caused about 800,000 admissions and 24,600 deaths. Recent progress made in studies dealing with influenza, the common cold, and pneumonia suggests that eventually it may be possible to immunize troops against certain of these infections. It also seems probable that the use of chemotherapeutic agents may cause a reduction in their mortality.

Diphtheria and scarlet fever are less important as military hazards, and specific biologicals are available for their prevention and treatment, but their epidemic appearance among troops may give rise to annoying and perplexing administrative problems. Similar problems arise with the occurrence of measles, of which there were 98,000 cases during the World War, and of mumps, which though numerically unimportant ranked third as a cause of lost time. The control of meningococcus meningitis, which was relatively infrequent but an important cause of death, is not considered satisfactory. In fact, it appears that the elaborate meningococcus carrier surveys which were conducted during the war may have been useless. The effectiveness of vaccination against smallpox is indicated by the fact that during the last war the incidence of this disease was negligible (0.5 per 1000) and there were no deaths.

(5) *Insect-Borne Infections.* The insect-borne diseases probably have been just as important as the intestinal or respiratory infections in shaping the twisted course of human history. Since the earliest times armies operating in countries afflicted with endemic malaria, yellow fever, typhus fever, or plague have been attacked and crippled by epidemics of these diseases.

Our World War experience fails to indicate their potential military significance. The admission rate for malarial fevers was 3.7 per 1000, with practically no deaths; there were only two cases of typhus, and both yellow fever and plague failed to appear. Unfortunately, this low incidence cannot be ascribed to the use of specific control methods, as it was due largely to chance or the absence of these diseases from the regions occupied. In the future we may not be so fortunate and, therefore, better methods should be developed for the control of insect-borne diseases in the field. Theoretically this is possible, since much information concerning the mechanism of their

transmission is now available. Practically it is difficult, because troops engaged in field duties have little or no time for insect control, and prophylaxis must depend on methods which protect soldiers against the bites of infected vectors or the organisms which they transmit.

In malarious regions troops can be kept on their feet and free from clinical malaria by the daily prophylactic use of quinine, but this drug simply delays the appearance of the disease during its use and does not prevent infection. Atabrin, plasmochin, and other chemicals are now being investigated in the search for a better field prophylactic. Since the discovery of jungle yellow fever in South America, this disease is again recognized as a serious menace to troops, and it is hoped that the vaccine now being tested in Brazil and elsewhere will be found to be effective. Various plague vaccines have been proposed and tried, but their specific military value has not been demonstrated. The delousing of troops, which was employed during the World War, is not considered adequate for the prevention of typhus. Therefore, the new rickettsia vaccines now being tested are of great interest to those concerned with military preventive medicine.

In concluding this talk it is desired to emphasize the following facts:

(1) Since the middle of the last century there has been a remarkable improvement in the medical care afforded the American soldier, and it is now possible to protect him against certain diseases which formerly menaced his health and life.

(2) Beginning with the pioneer discoveries of Pasteur, Koch, and Lister, each step in this tedious advance in military medicine has been made possible by some new fundamental truth discovered through the painstaking efforts of a host of investigators working in the laboratories and hospitals of the world.

(3) There are still many serious diseases against which we are unable to protect troops, and the urgent need for effective control methods is a challenge not only to the Medical Corps of the Regular Army, but to every physician in the United States.

(4) When one considers the satisfactory results obtained through the enormous expenditures so wisely made for the development of more effective munitions, and when one realizes that every improvement in disease control which we now enjoy is the direct result of scientific investigation, it seems obvious that a comprehensive program for research in military preventive medicine deserves an important place in our plans for national defense.

RESULTS OF THE USE OF EXTRACT OF THE INTESTINAL MUCOSA IN THE TREATMENT OF VASOMOTOR RHINITIS*

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For many years it has been suspected that histamine has a rôle in the allergic reaction. If this is true, a substance having the ability to detoxify histamine would seem to have useful therapeutic possibilities in the treatment of allergic conditions. An intestinal extract † said to have such detoxifying properties against histamine, has been supplied to us for therapeutic trial in the treatment of allergic conditions and this paper deals with our preliminary clinical observations in the use of this product.

Only a few of many important experimental and clinical observations on the rôle of histamine in relation to allergy and anaphylaxis and on the histamine-detoxifying extract (histaminase) will be referred to in this brief report. In 1910, Dale and Laidlaw reported that the injection of a small amount of histamine intravenously into a guinea pig would cause symptoms and postmortem findings similar to those described by other workers when they injected peptone into the circulatory system of a peptone sensitized guinea-pig. Lewis and Grant, in 1924, noted that stroking the skin of a normal person or especially of one who had factitious urticaria would produce a cutaneous response similar to the response to histamine when this substance is punctured into the skin. These investigators concluded that injury to the skin liberated a chemical substance which had a histamine-like action that was responsible for the formation of a wheal by its effect on the vessels and nerves.

Another significant observation was that of Hare who demonstrated, in 1926, that the reaction of the skin of allergic patients to specific proteins was almost identical with the cutaneous response to histamine. These and other similar findings suggest that histamine plays some part in conditions of allergy and anaphylaxis. Also these findings support the views of Lewis and Dale each of whom had been led to believe that the allergic reaction was due to the interaction of the antigen and antibody in or on the cells and that this interaction caused the formation or liberation of either histamine or of a histamine-like substance which, in turn, was responsible for the symptoms owing to direct action on the cells of the body. The isolation of the H-substance from the blood of rabbits and its identification as histamine by Code and Ing and the subsequent demonstration by Code that histamine is to be found in comparatively large quantities during anaphylaxis in certain ani-

* Submitted for publication February 13, 1939.

† The extract used in this study was courteously supplied by the Department of Medical Research, Winthrop Chemical Co.

mals support the previous hypotheses that in conditions of anaphylaxis and allergy histamine plays an important part.

In 1929, Best demonstrated the presence of a histamine-inactivating material in the lung and in other tissues of the animal body. Further information concerning the action, properties and distribution of this substance was presented by Best and McHenry in 1930, who then found that in dogs the histamine-inactivating material was found in largest amounts in the small intestine and kidneys, that a moderate amount was present in the lungs and blood and that very little was present in the skeletal muscles, liver and spleen. Because this substance seemed to possess many of the characteristics of an enzyme, Best and McHenry gave it the name "histaminase." This substance, they thought, exerted its enzymatic action on the histamine molecule by rupturing the iminazole ring, thus bringing about a change such as to cause the histamine to lose its usual physiologic action.

In recent years there has been available in Europe a preparation which is an intestinal extract and which has properties said to be similar to those of the "histaminase" of Best and McHenry. Reference to a great number and variety of conditions, both allergic and nonallergic which have been treated with this substance with startling and almost uniformly good results may be found in German literature. Roth and Horton of The Mayo Clinic reported on March 3, 1937, very favorable results in the treatment of patients hypersensitive to cold with this preparation, and more recently Foshay and Hagebusch stated that this substance will lessen materially the severity and shorten the duration of serum sickness.

The use of this intestinal extract therapeutically for vasomotor rhinitis was reported first by Adelsberger in October, 1937. He reported very favorable results in the treatment of a group of 39 allergic patients, eight of whom had allergic rhinitis. Five of the latter were cured completely, the condition of one patient was improved and two were unable to notice any change in their symptoms. Although the substance was used by us occasionally in the treatment of a number of other allergic conditions, this report concerns our experience with its use in the treatment of vasomotor rhinitis only.

Vasomotor rhinitis was chosen for study for several reasons. It is a common condition and the nasal membranes could be observed before and after the substance was administered. Therefore, this condition gave an opportunity for deriving objective as well as subjective evidence of the effect of the substance administered. Also, certain cases of vasomotor rhinitis are encountered which are due to or are suspected of being due to sensitiveness to food and because the preparation is an intestinal extract, it was felt that it might be more effective in cases of allergy to food than in cases of allergy caused by inhalants or physical agents. There are many cases of vasomotor rhinitis, however, in which it is impossible to prove that allergy is an etiologic factor, although in all other respects they appear to be identical with allergic rhinitis. We are well aware of the difficulties of drawing con-

clusions relative to the effectiveness of any remedy in the treatment of a condition such as vasomotor rhinitis or, indeed, of any other allergic condition. We know full well that in such cases spontaneous remissions of symptoms occur for no known reason and that there is a tendency for uncomplicated vasomotor rhinitis to improve over a sufficient period of time. Having borne these facts in mind, we feel that the results to be reported are at least conservative, if not conclusive.

Procedure

The routine procedure consisted of having the patient take orally one or two (usually two) tablets of the extract ten minutes before each meal.* In cases in which this amount was felt to be ineffective, the dose was raised to four tablets before each meal before discontinuing its use altogether. Because the supply of material was limited, the administration was not continued beyond seven to fourteen days among those patients who failed to be relieved by the aforementioned procedure. An attempt has been made to keep those patients who were relieved supplied with quantities of the material sufficient to keep them comfortable.

Twenty-nine patients who had vasomotor rhinitis were observed in this study. In 19 of the cases there was sufficient evidence in the results of cutaneous tests and in the clinical histories to suggest that the nasal symptoms were aggravated by the ingestion of specific foods. The remaining ten patients had vasomotor rhinitis which had been resistant to other forms of treatment. Nasal obstruction was constant in 19 cases and intermittent in 10 cases. Eight patients were males, 21 were females and their ages ranged from 10 to 59 years.

Of the 29 patients, 12 (41.3 per cent) were relieved of the nasal obstruction, watery discharge and sneezing. Of the patients who gained relief, a definite improvement in the appearance of the nasal membranes could be seen. The condition of four patients (13.7 per cent) apparently was improved, but not to the extent experienced by the 12 previously mentioned. The remaining 13 patients (44.8 per cent) did not receive appreciable relief of the nasal symptoms. In certain of the cases in which relief seemed to occur at first, subsequent inquiry revealed that, later, benefit failed to be obtained from the treatment. Failures in the use of a remedy are usually more accurately evaluated than degrees of improvement. In these instances, however, in which the dosage and duration of administration are not well standardized and in which the material administered varies in potency, the evaluation of results may not be entirely accurate. Before considering the question of variation of the material used, the records of three cases in which benefit was derived from the use of this extract will be reviewed.

*Each tablet represents five histamine detoxicating units. One unit represents the quantity of extract which is capable of detoxicating 1 mg. of histamine in 24 hours at a temperature of 37° C.

Case Reports

Case 1. A woman, aged 24 years, complained of symptoms of vasomotor rhinitis and mild asthmatic wheezing. She began treatment with the intestinal extract in March, 1937. The typical symptoms of vasomotor rhinitis began in 1933 and after a study from the point of view of allergy by her home physician, followed by the prescribing of a dietary regimen which involved a process of elimination of certain foodstuffs together with the administration of calcium, her condition improved; but later the remedial measures became ineffective. In September, 1936, nasal ionization elsewhere resulted in almost complete relief for 12 weeks. The symptoms gradually returned to their previous degree of severity and there were never periods longer than 12 hours during which she was free of symptoms. At that time there did not seem to be any relation between the nasal symptoms and ingestion of any special foods. Asthmatic wheezing occurred during exposure to cold and after moderate exercise.

Physical examination was essentially negative except for bilateral, nasal obstruction. The nasal mucous membranes were characteristic of the allergic type. Roentgenologic examination of the sinuses showed evidence suggestive of chronic pansinusitis with thickened membranes, secretion in the left antrum and polyps in the left side of the nose. Roentgenologic examination of the thorax gave negative results. An eosinophilia of 10.5 per cent was present. All cutaneous tests with air-borne and food allergens gave negative results. The administration of two tablets of the extract ten minutes before each meal brought about remarkable relief after the first few days and other types of treatment were not required to keep the patient comfortable, for the period of several months during which we were able to follow her case. Relapses occurred when the administration of the preparation was discontinued.

Case 2. A Jewess, aged 38 years, came to the clinic for the first time in 1933 and complained of constant nasal obstruction, copious, thick, yellowish, purulent nasal discharge, frequent frontal headaches and many attacks of bronchitis associated with moderately severe asthma each winter since the age of 18 years. An operation on the tonsils had been performed three times. She had had a bilateral external operation on the maxillary sinuses in 1926. Examination revealed evidence of widespread infection of the paranasal sinuses. Allergic studies gave negative results. Local treatment to the nasal membranes gave but temporary relief.

On November 4, 1938, the patient returned and complained that nasal symptoms were not relieved but that the bronchitis and asthma had been relieved greatly after she had spent the intervening winters in Florida. She had observed that ingestion of spaghetti, sago, tapioca, salmon and salted herring would aggravate the nasal obstruction and discharge. These foods had been eliminated from her diet. Nasal examination revealed that the mucous membranes were full, edematous and pale and that a heavy mucoid secretion was present in each nostril. The inferior turbinates were hypertrophic and they blocked the nasal passages. Washings from each maxillary sinus did not show evidence of infection. Allergic cutaneous tests for inhalants and foods were repeated, but all gave negative results except for a reaction to beef which was graded 1 plus. Roentgenologic examination of the thorax gave negative results.

The patient was given two tablets of the intestinal extract before each meal and after the first day "wonderful" improvement was noticed. The nasal discharge and obstruction had disappeared by the second day of treatment and the patient stated that she had not been able to breathe so well in 20 years. On the third day, the examination showed that the nasal passages were open, the mucous membranes were less edematous than formerly, were dusky in color and the secretions appeared normal. She has remained free of symptoms while using the extract.

Case 3. In January, 1937, a woman, aged 38 years, began treatment with the intestinal extract. She had been a patient at the clinic frequently since 1934 for treatment of nonseasonal allergic rhinitis and ragweed hay fever. For many years

she had complained of nasal obstruction, watery discharge and frequent sneezing, but recently these symptoms had become more distressing than formerly. She would awaken about four o'clock in the morning and would sneeze for two to three hours. Relief was not experienced in different bedrooms, in a pollen-free room or in different parts of the United States and Canada, but she was entirely free of symptoms in Europe and on board ship. The symptoms returned a few hours after her arrival in New York. Ingestion of lettuce, peas and oranges was known to increase the severity of the nasal symptoms. Amytal would cause severe itching and generalized hives. A carefully controlled diet based on a process of elimination of suspected foodstuffs under the supervision of a dietitian and desensitization to pollens had failed to give relief. Cutaneous allergic tests for manifestations toward inhalants and foods revealed many positive results to each group. The greatest reactions were obtained by testing with ragweed, red root, maple, poplar, whole wheat, crab, lobster, tea, navy beans, tomato, turnip, parsnip and lettuce. The administration of three to six tablets of the intestinal extract the day before a meal which contained foods known to aggravate her nasal symptoms never failed to control the distress. When administration of the preparation is discontinued the symptoms return.

Comment

Certain inconsistencies in the reactions of patients to this material were noted almost from the first. Some individuals already referred to seemed benefited at first and later did not receive benefit. Other individuals who seemed definitely benefited by the extract prepared for oral use, were not benefited when given a similar preparation prepared for intramuscular use, although Foshay and Hagebusch stated subsequently that they had found the latter preparation equally as efficient in relieving serum sickness as the oral preparation. This variation in material was apparent to one of the patients who was able to distinguish between tablets from different consignments by their effect on his symptoms. At our request, Dr. Charles Code at the Institute for Experimental Medicine tested in vitro one consignment of the material for its histamine-destroying properties and no such effect was found. There is, then, both experimental and clinical evidence to suggest that a variation in the potency of the intestinal extract exists and that the results of this study and, perhaps, the results of other series of observations should reflect such variations.

It seems obvious that conclusions may not be drawn at this time from this study. Although many of the patients selected for treatment were not benefited, the relief experienced by other individuals seemed so definite and so remarkable that the use and further study of this product in cases of vasomotor rhinitis and allergic conditions of known or unknown etiology are warranted. Also, definite evidence is not forthcoming from our studies that allergic rhinitis due to ingestion of foods responds better to the administration of the extract than does allergic rhinitis due to other causes. We are still unable to predict which patients who have vasomotor rhinitis will obtain relief from the use of this material. The matter of dosage remains unsettled. Information is lacking as to how or where the material is absorbed from the intestinal tract and the time necessary for its action is not known.

Neither is there evidence that the benefit, when it occurs, is attributable to the activity or content of an enzyme, although at the present time this hypothesis offers the best explanation of the action of the extract. Although the use of this intestinal extract in the treatment of vasomotor rhinitis seems to have definite promise, a more accurate clinical evaluation of this product must await additional work which is in progress.

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CLINICAL DESENSITIZATION TO WHEAT BY USE OF AN ACETYLCHOLINE DERIVATIVE*

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THE focal reactions which result in the clinical syndromes of bronchial asthma, vasomotor rhinitis, eczema, urticaria and angioneurotic edema occur in tissue which is supplied by the cholinergic division of the autonomic nervous system. The peripheral mechanism which produces these symptoms may be initiated or exaggerated by different stimuli such as the antigen-antibody reaction of allergy, local irritation, infection, autonomic nervous reflex, and emotion or psychogenic stimuli. It is frequently possible to reproduce at will the particular symptom to which a hypersensitive individual is susceptible by small doses of acetylcholine or its derivatives. Hundreds of methods of altering the status quo of the bodily reactions resulting at least in temporary alleviation of the above symptoms in a few individuals have been reported. The state of local tissue reactivity may also be altered in selected individuals and the symptoms controlled by repeated cholinergic stimulation. This method of therapy is particularly significant because it is in accord with the new knowledge of the chemical transmission of nerve impulse, a concept which will influence future study of many functional disorders.

In a group of seven patients who were proved to be allergic to the ingestion of wheat, the original symptoms were reproduced by the acetylcholine derivative, acetyl-beta methyl choline chloride (mecholyl). This chemical was then administered daily for 20 to 60 days in increasing dosage according to the tolerance of the individual during a controlled symptom-free period. When wheat was readded to the diet of these people, the original symptom did not recur and they have remained well or greatly improved under observation for one year or longer. In four cases previous attempts to desensitize with wheat extract had been unsuccessful and in two, previous treatment with repeated injections of histamine had not influenced the course of the illness.

CASE REPORTS

Case 1. W. A., a 23-year-old nurse. When first seen on July 5, 1937, she complained of nasal congestion and blocking, sneezing, severe cough with wheezing; all symptoms were of three years' duration. Examination revealed pale, boggy swelling of the nasal mucous membrane and wheezing râles in the chest. Nasal secretion and sputum contained chiefly eosinophile cells. Intradermal skin tests for common offending substances were entirely negative. The symptoms subsided on a milk, egg and wheat free diet and did not recur when milk and egg were readded to the diet. When wheat was added all original symptoms returned within 48 hours and promptly

* Delivered before the Central Society for Clinical Research, Chicago, November 6, 1938.
Mecholyl for this work was supplied through the courtesy of the Merck Laboratories, Rahway, N. J.

subsided when wheat again was withdrawn. Symptoms recurred occasionally during the next seven months due to her inability to follow a wheatless diet. Meanwhile an attempt was made to cause her to gain tolerance for wheat by adding it to the diet in small increasing quantities. On April 9, 1938, 8 milligrams of mecholyl were given by injection. This caused flushing, lacrymation, salivation, blocking of the nose, cough, chokiness and wheezing. These symptoms could be stopped within 30 seconds by applying a tourniquet above the site of injection and would recur within 15 seconds after the tourniquet was released. Symptoms persisted for about 20 minutes. On April 10 daily injections of mecholyl were started beginning with 0.5 milligram and increasing 0.5 milligram daily as tolerated. On April 30, 8 milligrams were again given and the general reaction was distinctly less than that caused by the original dose. Wheat was resumed in the diet on May 15 without recurrence of symptoms. Since that time she has continued to eat wheat and occasionally experiences some wheezing, but she can abort the symptom by an injection of mecholyl. She continued giving herself 5 milligrams of mecholyl weekly for two months. During the past year she has eaten everything and remained symptom-free.

Case 2. E. E. W., a 24-year-old man, a bookkeeper. When first seen January 25, 1938, he complained of spontaneous swellings of the hands, tongue, face, and feet, of three years' duration. On examination he appeared in excellent health. Laboratory findings were not significant. Intradermal skin tests were all negative except that a definite latent positive test with wheat extract was obtained. There was a wide zone of itching erythema present after 24 hours. The swellings subsided within 48 hours after wheat had been stopped in the diet. Swellings recurred when wheat was added to the diet for trial. Injections with wheat extract in increasing quantity were given from February 14 until April 12. Very small quantities of wheat were then started by mouth. Swellings recurred on April 22 when he was eating only one small saltine cracker daily. Daily histamine injections were given from April 10 to May 5. Small quantity of wheat again caused swellings to appear. On May 17, 1938, he was given 10 milligrams mecholyl which caused flushing, salivation, etc., and appearance of swelling on one arm. On May 18 injections of mecholyl were started with 0.5 milligram and increased 0.5 milligram daily. Five milligrams were all he could tolerate without discomfort and this dose was continued for one month. Occasionally swellings would appear soon after an injection, otherwise he was well. Wheat was resumed July 15. Swellings did not recur. On August 10, 1938, a few swellings recurred and mecholyl injections were resumed and were continued twice weekly (five milligrams). He had one attack of spontaneous edema in July 1939. Mecholyl (5 mg.) was again given for one month. Since that time his swellings have been negligible although he eats wheat regularly.

Case 3. F. S., a 25-year-old merchant's wife. Complaints at time of original examination on December 11, 1936, were attacks of sudden swelling of face, feet, hands and elsewhere, attacks of sneezing and nasal blocking, severe attacks of cough with wheezing and attacks of vomiting of six months' duration. Examination revealed swollen, pale, boggy, nasal mucous membrane, angioneurotic type swelling of face, wheezing râles on forced expiration. Laboratory work revealed nothing significant except eosinophile cells in the nasal secretion. Intradermal skin tests for common allergens were all negative except the wheat test which caused a latent reaction, an erythematous area, three cubic centimeters in diameter which persisted for several days. Symptoms subsided promptly upon withdrawal of wheat. A series of injections with wheat extract were given in 1937 followed by readdition of wheat to diet in infinitesimal quantity. After one full slice of bread was reached she began having nasal congestion and cough. Swelling of the face recurred at intervals, due to inability to avoid wheat entirely during 1937, and became quite severe in April, 1938. A strict wheat free diet was resumed. An injection of 5 milligrams of mecholyl was given on April 23 which produced, within a few minutes, sneezing, cough and wheez-

ing. Mecholyl was then given daily beginning with 0.5 milligram and increased 0.5 milligram with each subsequent injection. On May 15, 1938, 5 milligrams of mecholyl caused some salivation and tightness in the chest but not as much reaction as previously. Wheat was resumed in the diet as desired on May 20, and to date symptoms have not recurred.

Case 4. E. C., a 51-year-old farmer's wife. Her complaints on March 4, 1938 were the occasional recurrence of an eczematous rash on her arm for many years, a continuous eczematous facial rash of two years' duration and periodic swellings of the face for five months. On examination the eczema was found to be chiefly of flexual distribution with overflow on the thighs and on the ears. Laboratory work revealed no significant findings except blood eosinophilia. An intradermal skin test with wheat extract gave a latent positive test. Other tests for common allergens were negative. The swellings did not recur and the rash promptly subsided when wheat was eliminated from the diet. On March 18 wheat was added to diet. Two days later the rash reappeared and wheat was again stopped. She was given injections with wheat extract in increasing dosage from March 21 to April 15 when the injections were found to cause a flare-up of the eczema. On April 30 she was given 10 milligrams mecholyl which caused swelling of the face and next morning the rash was present in old areas on the arms. This course of events was repeated on May 6 and 7 thereby proving that eczema could be induced by mecholyl. On May 10, 0.5 milligram mecholyl was given and the dosage was increased 0.5 milligram daily if tolerated. On June 17, 10 milligrams mecholyl were given without causing swellings or recurrence of eczema. Wheat was again eaten on June 20 without causing any disturbance. Mecholyl was given weekly until August 1, 1938. There has been no recurrence of the original trouble to date although she eats some wheat daily.

Case 5. E. F., a 35-year-old woman, a stenographer. When first seen, on August 5, 1937, she complained of daily recurrences, for three years, of swollen areas which itched. Examination revealed nothing significant except large urticarial wheals and small erythematous areas. Laboratory work revealed nothing significant. Intradermal skin test with wheat extract gave a latent reaction about the size of a silver dollar within 24 hours. Other tests were negative. The swellings subsided entirely upon the withdrawal of wheat. A series of wheat injections was given and several attempts to add wheat in small increasing dosage resulted in recurrence of hives. On February 2, 1938, histamine injections were started and increased daily until 0.5 milligram was reached. The swellings continued to recur when wheat was eaten. On April 11, 8 milligrams mecholyl were given and produced much flushing, sweating, salivation and a few wheals. Mecholyl injections were given daily beginning with 0.5 milligram and increasing 0.5 milligram daily as tolerated. The usual dose was 3 milligrams. Wheat was readded to diet on May 24 without reproducing wheals. Since that time bread has been eaten as desired. Occasionally she has a few hives but these can be controlled by taking one or two injections of mecholyl weekly.

Case 6. R. S., an eight-year-old feeble minded boy of indigent family. Complaints when first seen, November 23, 1937, were asthma and nasal blocking of three years' duration. The asthma has been continuous throughout the year with aggravation by "colds" in winter. He was in St. John's Hospital from November 15, 1937 until January 15, 1938, during which time he was found to have allergic asthma and bronchial infection. Intradermal skin test for wheat was immediately positive with wheal formation. After subsidence of infection and elimination of wheat his symptoms stopped. Asthma recurred on February 9 when wheat was added to diet. Symptoms subsided within two days after withdrawal of wheat. Occasional flare-ups recurred in March and April when wheat was eaten. On April 12, 1938, he was given 5 milligrams mecholyl which caused much salivation and severe bronchospasm. Mecholyl was given regularly beginning with 0.5 milligram and increased 0.5 milligram every other day. After 5 milligrams were reached this dose was continued and

usually caused some wheezing. On June 15, 1938 wheat was again added to the diet but asthma did not recur. Weekly injections of mecholyl (5 mg.) were continued for two months. He had had no recurrence of asthma when last seen in August 1939.

Case 7. E. W., a 25-year-old school teacher. Her complaints on May 21, 1937, were perennial attacks of headache, vomiting, and asthma, with severe exacerbation in the autumn, of seven years' duration. Examination revealed nothing significant except wheezing râles at every examination. Intradermal skin tests were strongly positive to ragweed and to wheat. After the pollen season had passed it was found by repeated trial that she could remain free from asthma by elimination of wheat from her diet and that when this food was added some wheezing would recur. On April 9, 1938, she was given 8 milligrams of mecholyl and developed marked flushing, salivation, and severe bronchospasm. Daily injections of mecholyl were started on April 10 with 0.5 milligram and increased 0.5 milligram daily if tolerated. Regular dosage of about 3 milligrams was all that she could take without wheezing. After June 4 injections were given weekly until August 1. There was some recurrence of asthma during the ragweed season but only about 25 per cent as severe as that experienced in previous years. Preceding the ragweed season in 1939 mecholyl was given along with desensitizing injections of ragweed pollen extract and almost 100 per cent relief was obtained.

Discussion

The terms cholinergia and adrenergia are now in general use signifying imbalance of autonomic nerve activity. Patients who have a tendency to develop asthma, eczema, vasomotor rhinitis, urticaria and angioneurotic edema often demonstrate other features of cholinergia such as excessive sweating, salivation, indigestion of hyperacidity type, spastic bowel and dermographism. The cholinergic state in itself seldom causes distress; it is for the superficial symptoms that relief is sought. Adrenergic stimulants usually produce prompt but temporary relief from this group of cholinergic symptoms. Therapeutic measures should be directed against excessive action of acetylcholine itself. If choline esterase, the enzyme which normally causes immediate destruction of acetylcholine in the tissues, could be prepared and administered in a manner to diminish acetylcholine action it might be of some value. If the action of the choline esterase normally present could be made more effective a farther step in the right direction would be accomplished. By daily cholinergic stimulation with mecholyl we may be stimulating more efficient esterase action. Some degree of tolerance for cholinergic stimulation is, certainly, gained in some manner.

The question naturally arises concerning the interrelationship of acetylcholine and histamine. Histamine is probably released in the body tissues as a result of trauma, whereas acetylcholine is a normal physiologic stimulant. Acetylcholine is thought to act on arterioles causing their dilatation and histamine action is on the capillaries, probably making their walls more permeable. If histamine is injected in large dosage or is produced in hypersensitive individuals by trauma an anaphylactoid reaction results which probably disturbs the acetylcholine-choline esterase balance in certain shock organs. It is also probable that excessive acetylcholine action causes the liberation of histamine. Much work will be necessary to enlighten this problem.

Mecholyl has been used in a wide variety of allergic and exudative disorders in order to determine its limitations. It has been found to be most effective in aborting cases of angioneurotic edema, urticaria, and asthma in which the specific exciting factor could be determined and eliminated during the period when treatment with mecholyl was started. Mecholyl, if given repeatedly, usually causes allergies which are of continuous nature to become worse. I have not found mecholyl to be of value in the treatment of contact dermatitis and it is of doubtful value in cases of inhalant allergy.

The effects of this acetylcholine derivative when given in the manner we have described is probably superficial and although the status quo is altered there is little change in the basic hypersensitive or cholinergic states. Fundamental alterations in the method of living, working, eating and thinking may be necessary to enable the autonomic nervous system to readjust itself.

THE CLINICAL APPLICATION OF THE DETERMINATION OF CIRCULATION TIME *

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THE estimation of the circulatory status of a patient is one of the most important problems the physician is called upon to face. Dyspnea, basal râles, tachycardia, hepatomegaly and peripheral edema usually indicate the presence of cardiac failure. But one may at times be sorely perplexed in determining whether the dyspnea complained of is cardiac, pulmonary or extrathoracic in origin; or whether the obvious pleural effusion is due to heart disease, thoracic tumor, malnutrition or hypertension.

Two of the factors influencing the maintenance of circulatory efficiency are the minute output of the heart, and the velocity of blood flow. The estimation of the cardiac output is still a rather technical and complicated procedure. But beginning with the work of Blumgart and his associates [1] in 1927, increasing interest has been paid to the study of the velocity of blood flow. The determination of the velocity of blood flow involves measuring the time required for the passage of a foreign substance from its point of introduction in the blood stream, until its arrival at another part of the body.

In a recent article, we [2] have discussed the progress made during the past decade in simplifying this test of cardiac function. What was once a highly complicated laboratory study, demanding expensive equipment and technical skill, is today a very simple procedure. So much have the methods for determining circulation times been improved, that they can be done inexpensively and with ease at the bedside or in the office. We propose in this paper to present again the technic adopted for determining circulation times, and cite a few examples of their wide clinical application.

METHOD

With the patient in a recumbent posture, the calcium gluconate arm-to-tongue time is determined. A slight modification of the method originally described by Goldberg [3] is used. With the arm at the level of the right auricle an 18 gauge needle attached to a syringe containing 10 c.c. of 20 per cent calcium gluconate,† is inserted into an antecubital vein. Four cubic centimeters of this solution are then rapidly injected, the "end point" being a sensation of heat in the back of the throat and tongue. The wave of heat then spreads to the face, abdomen, perineum and extremities. The injection is timed by a stopwatch, from the instant it is begun until the moment the sensation of heat is felt in the throat. A duplicate reading is made within

* Read at North End Medical Society, April 28, 1939.
Received for publication July 18, 1939.
From the Wards and Outpatient Departments of Jewish Hospital, Philadelphia.
† Neo-Calglucon, supplied by Sandoz Chemical Works, Inc.

two or three minutes. With the same needle in situ or by another venipuncture, the ether arm-to-lung time is determined. This test, originally described by Hitzig,[4] consists of the intravenous injection of a mixture of five minims of ether and five minims of saline; the " end point " is the perception of ether vapor in the upper respiratory passages. Almost invariably the patient will cough, grimace or denote by sour facial expression the presence of the ether. Again, the injection is timed from the beginning to the moment the " end point " is recognized.

The Normal Circulation Time

The range of normal circulation times given by different observers has varied according to the methods used. But in the last few years, with improvement in the technic and refinement of the agents used, the results obtained have shown a surprising uniformity.

The ether time is a measurement of the time necessary for the ether to pass from the antecubital vein through the superior vena cava and right heart to the pulmonary artery and lungs. Ether is so readily diffusible that the time required to reach the upper air passages is negligible. The ether arm-to-lung time is therefore an index of the functional activity of the right heart. We [2] have corroborated the results of Hitzig [4] and others, who showed the normal arm-to-lung time ranged from 3 to 8 seconds.

Various substances have been suggested for determining the arm-to-tongue time. Decholin,[5] saccharin [2, 6] and more recently, calcium gluconate [2, 3] and magnesium sulphate [7] have been used. Irrespective of the agent, the arm-to-tongue time is that required for the injected material to pass from the antecubital vein through the right heart, the lungs, the left heart, the aorta and its branches, to the tongue. The velocity of blood flow from aorta to tongue is very rapid, so that the difference between the ether arm-to-lung time and the arm-to-tongue time is an accurate measure of left heart circulation. The determination of the left heart time is one of the best methods available for estimating the velocity of pulmonary blood flow. Normal arm-to-tongue times have been found to range from 8 to 16 seconds, irrespective of the method used. We agree with Goldberg that the calcium gluconate method is the most desirable to date for determining the arm-to-tongue time.

In tables 1 and 2 are listed the values obtained in patients by the ether and calcium gluconate methods.

The Circulation Times in Various Abnormal States

Cardiac Disease. Perhaps the widest application of these procedures is in the diagnosis of cardiac disease. With the development of cardiac failure, the circulation time becomes prolonged. Since the introduction of the ether arm-to-lung test by Hitzig, a number of papers [8] have appeared confirming the value of this test in the diagnosis of right heart failure. This

TABLE I

	Cases	Circulation Times—Ether	
		Range (Sec.)	Average (Sec.)
Normal	169	3.0–9.0	5.8
Pulmonary Disease	24	4.0–9.0*	6.1
Cardiac Disease			
Without Failure	32	4.0–9.0	6.3
With Failure	44	7.0–19.0	10.2

* One patient with chronic fibroid phthisis had an ether time of 10.0 seconds.

TABLE II

	Cases	Circulation Times—Calcium Gluconate	
		Range (Sec.)	Average (Sec.)
Normal	133	8.0–16.5	12.3
Pulmonary Disease	35	8.0–16.0*	11.5
Cardiac Disease			
Without Failure	36	8.5–17.0	13.1
With Failure	46	16.0–55.0	24.6

* One patient with unilateral functioning lung had a time of 7.5 seconds.
One patient with chronic bronchial asthma had a time of 20.0 seconds.

procedure is safe, accurate, and easily carried out. With rare exceptions, an ether time within the range of normal is evidence against the presence of right heart failure. In right heart failure of course, this time is prolonged. In addition, the comparison of the ether and calcium gluconate times is of value in localizing the part of the circulation in which blood flow is retarded.

Of even greater value in the diagnosis of cardiac failure, is the estimation of the arm-to-tongue time. The fact that the normal circulation time with decholin,[5] saccharin [2, 6] and calcium gluconate [2, 3] averaged 12 to 13 seconds with all three methods, attests to the accuracy of the test. Since the circulation time is usually prolonged beyond 16 seconds in cardiac failure, the application of this test to the differential diagnosis of cardiac disease becomes apparent.

Blumgart and Weiss [1] stated that prolongation of the circulation times almost invariably indicated the presence of congestive heart failure. Tarr, Oppenheimer and Sager [5] found that in patients with congestive heart failure, the velocity of blood flow averaged 26 seconds, approximately double the normal average. Our work [2, 9] has added confirmatory evidence to these findings.

Circulation times in heart disease are shown in tables 1 and 2. Below are cited a few cases indicating the use of the tests in the diagnosis of heart disease.

Case Reports

Case 1. Mrs. I. M., aged 22, was admitted to the maternity ward showing marked dyspnea, moist râles at both bases, a double mitral murmur, regular tachycardia of 120, enlargement of the left border of the heart to the anterior axillary line, and obvious peripheral edema. There was a history of a number of attacks of rheumatic fever. The diagnosis of cardiac decompensation complicating pregnancy was made. However, in view of the presence of polyhydramnios and a twin pregnancy, the cardiac consultant felt that the dyspnea, râles and edema were mechanical rather than cardiac in origin. He therefore advised against a Caesarean section. Circulation times were done, and an ether time of 5.2 seconds with a calcium gluconate time of 14 seconds obtained. These circulation times were confirmatory of the absence of cardiac failure. The patient went into labor, easily delivered of twins spontaneously, and was well from then on. Repeated circulation times were normal.

Case 2. Mrs. C. H., aged 48, was admitted on a number of occasions, for recurrent attacks of edema of the legs, dyspnea, palpitation, precordial discomfort and abdominal enlargement. Examination revealed a moderate hypertension, bilateral massive pleural effusion, ascites, and anasarca. Laboratory studies led to a diagnosis of chronic diffuse glomerulonephritis, though some of the staff felt the case was one of true lipoid nephrosis. In view of the extreme dyspnea and anasarca, the possibility of cardiac failure was entertained. Circulation times, despite the extreme dyspnea and hydrothorax, were perfectly normal. (Ether time—5 seconds; calcium gluconate time—11 seconds.) Necropsy later revealed a chronic lipoid nephrosis.

Case 3. Mr. B. G., aged 51, was admitted with a history of severe precordial pain, tachycardia and cyanosis. There was no evidence of pulmonary congestion or cardiac failure. A clinical diagnosis of acute myocardial infarction was made and an electrocardiogram revealed in addition, an auricular flutter. Circulation times were performed within 48 hours of admission, and indicated a normal ether time, but a saccharin arm-to-tongue time of 24 seconds. This suggested the existence of cardiac failure, which, however, was not apparent by physical examination. The following day obvious cardiac decompensation was found, with pleural effusion, râles, and cyanosis. Circulation times done one month later were completely normal, and the clinical evidence of failure had disappeared.

The test is of further value in observing the response of patients with obvious cardiac failure to therapy.

Case 4. Mrs. G. S., aged 48, was admitted on a number of occasions, with recurrent attacks of cardiac failure. Studies indicated the presence of rheumatic heart disease, with auricular fibrillation, aortic stenosis, mitral stenosis and regurgitation, and chronic cardiac failure. Three days after her admission in October 1936, an ether time of 19 seconds and a saccharin time of 26 seconds were obtained, indicating severe right heart failure.

Following digitalization, bed rest and diuretics, the ether time in 12 days was reduced to 10 seconds and the saccharin and calcium gluconate times to 20 seconds.

Stewart and Heuer [10] have recently studied the cardiodynamics of adhesive pericarditis. Following pericardiectomy, prolonged circulation times (determined by the decholin method) returned to normal or almost normal limits, pari passu with the clinical and laboratory evidence of improvement.

Pulmonary Disease. A number of observers [11] have shown the value of determining the circulation time in the differential diagnosis of pulmonary disease. Circulation times are almost always normal in uncomplicated pulmonary disease. The use of these tests in the differential consideration of pulmonary and cardiac disease is obvious. We have repeatedly found normal ether and calcium gluconate times (despite the presence of dyspnea and cyanosis) in carcinoma of the lung, chronic fibroid phthisis, bronchial asthma, emphysema, lung abscess, empyema and pneumonia. In a number of our cases of bronchial asthma, calcium gluconate circulation times have not only been normal, but were in the low range of normal 8 to 9 seconds.[2] Charr and Savacool [12] have recently shown that the development of cardiac failure in cases of chronic pneumoconiosis is accompanied by the prolongation of the circulation times.

Disturbance in Metabolism. Reports have been published concerning changes in the velocity of blood flow in metabolic disorders.[13] It has been fairly well agreed that with hyperthyroidism there is an increase in the velocity of blood flow and a more rapid circulation time, whereas in myxedema, the arm-to-tongue circulation time is prolonged. For the past year or so, we [14] have been attempting to correlate the arm-to-tongue circulation time with the basal metabolism rate, but have not completely analyzed our data as yet. Our studies thus far do not indicate the clear cut correlation between circulation times and basal metabolism rates shown by previous observers.

As a rule however, hyperthyroidism is associated with a rapid circulation time, and myxedema with a delayed time. Tarr, et al.[5] have suggested that a normal circulation time in the presence of obvious cardiac failure should make one look for factors tending to increase the velocity of blood flow. A case in point can be cited.

Case 4. Mrs. M. S., aged 46, was admitted in extreme dyspnea, with edema of the legs up to the knees. The patient had had a diffuse toxic goiter removed 8 years previously. Examination revealed no thyroid enlargement, marked dyspnea, some cyanosis, hypertension, cardiac enlargement with rapid regular tachycardia, bilateral pleural effusion and edema of the legs. The diagnosis of hypertensive cardiovascular disease with cardiac failure was made, but the question of thyrocardiac disease was raised. A basal metabolic rate determination would, we felt, be too inaccurate. Four separate circulation times with calcium gluconate averaged 8 seconds, despite the obvious cardiac failure. A diagnosis of hyperthyroidism was made, the patient was placed on Lugol's solution and digitalis, and a thyroidectomy then performed. After a somewhat stormy course, she recovered and was discharged in excellent condition. Interestingly enough, her circulation time on discharge was 12 seconds, though her cardiac failure was gone.

Comment

The cases cited illustrate perhaps the more important applications of the determinations of circulation times. But with the awakening of interest in this procedure in the past few years, a number of other uses have been found.

The circulation time is rapid in anemia, and prolonged in polycythemia

vera.[15] Webb, Sheinfeld and Cohn [16] have studied the circulation time in surgical cases. They stated that patients with prolonged circulation times were poorer surgical risks and had higher operative mortalities. At this hospital, studies are being made of the effect of pregnancy, of spinal anesthesia and operative procedures, and of peripheral vascular disease, on the circulation times. It must be remembered that the circulation time test is only a measure of the velocity of blood flow; it cannot tell us how much work the heart can do. But as an aid in determining the circulatory status of a patient, or in the differential diagnosis of a number of conditions, it is quite a valuable procedure.

Summary

1. The technic of determining circulation times with ether and calcium gluconate is discussed.

2. In 169 normal patients, the ether arm-to-lung time ranged from 3 to 9 seconds, averaging 5.8 seconds.

3. The ether time is prolonged in many cases of cardiac failure. A normal ether time is against the presence of right heart failure.

4. In 133 normal patients, the calcium gluconate arm-to-tongue time ranged from 8 to 16.5 seconds, averaging 12.3 seconds.

5. The calcium gluconate time is prolonged in cardiac failure.

6. Circulation times in uncomplicated pulmonary disease usually fall within normal limits.

7. The value of circulation times in the diagnosis of cardiac failure, and in the differentiation of various clinical conditions is discussed.

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CARDIAC HYPERTROPHY; FORTY-TWO HEARTS WEIGHING 750 GRAMS OR MORE *

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VERY large hearts are noted occasionally in any autopsy series, and formerly were usually ascribed to the effect of one of the infectious types of heart disease. During 1937 and 1938 there were 1372 autopsies performed at the Vancouver General Hospital, and among these were found 42 instances of hearts weighing 750 grams or more. Analysis of this group shows that the infectious type of heart disease is less commonly the cause of hypertrophy of this extent than are degenerative changes. Since it was our intention to study only the so-called "cor bovinum" we arbitrarily chose a weight approximately twice the upper limit of normal heart size. In this connection it is interesting to note that our ideas regarding normal heart weight have undergone revision upward in the last 20 years. It was formerly thought that the upper limit of normal heart weight was 300 grams for men and 250 grams for women. Aschoff [1] showed that in men a normal heart might weigh up to 355 grams, and Parkinson,[2] in the Lumleian Lectures in 1936, quoted Dr. William Evans who gave as the upper limit of normal 12 oz. (360 grams) for women and 13 oz. (390 grams) for men. Smith [3] has shown that the size of the heart bears a constant relationship to the body weight, the ratio for males being 0.43 per cent and for females 0.40 per cent. These figures, he considers, are accurate for body weights between 100 and 210 pounds, with an error of only 8 to 10 per cent. The weight of the heart in a 200 pound man is by this method found to be 390 grams. Unless this fact is kept in mind we are apt to draw false conclusions from earlier analyses [4] where hearts weighing even less than 300 grams were described as hypertrophied. White [5] gives the normal as 0.40 to 0.45 per cent, with a range of from 0.35 to 0.50 per cent. Figures over 0.50 per cent can be safely regarded as showing hypertrophy.

The incidence of cardiac hypertrophy of the extent described in these cases is not easy to ascertain. Ophüls,[6] in a careful analysis of 3000 autopsies, mentions cardiac hypertrophy in association with arteriosclerosis in 10 per cent. Another 10 per cent showed endocarditis, and some of these would undoubtedly have shown hypertrophy. Further instances of hypertrophy occurred among cases of nephritis. The extent of the hypertrophy was not mentioned. Brines,[7] in an analysis of 1535 autopsies, found heart disease in 20 per cent and kidney disease in 14 per cent. Cardiac hypertrophy was mentioned only in the group showing coronary sclerosis, where it occurs in 50 per cent of the 46 cases. Grant,[8] in a follow-up study of 1000

* Received for publication July 12, 1939.

cases of heart disease over a ten-year period, noted 142 autopsies in the 470 deaths. Among these autopsies the heart weight was recorded in only 87 instances and in 26, or 29 per cent of these, the heart weight was more than 700 grams. If we apply Brines'[7] figures to our entire autopsy series we should have expected to find 274 cases of heart disease and 192 cases of kidney disease. The 42 instances of gross cardiac hypertrophy would, therefore, equal 9 per cent of the 466 cardiorenal cases, and 3 per cent of the entire series of 1372 cases. Boyd,[9] in an analysis of over 950 autopsies at the Toronto General Hospital in the years 1937 and 1938, found 85 cases showing cardiac hypertrophy. Of these only two were of 750 or more grams, and 10 of 650 grams or more in weight. Just why the incidence of extreme cardiac hypertrophy should be so much greater in Vancouver than in Toronto is not clear. It represents another instance in the peculiar geographical variation in pathological processes. The West is still a pioneer country, and the character of much of its industry is more strenuous than that of the East.

TABLE I

Report on Autopsies, 1937, Vancouver General Hospital

	Hospital Deaths						Total	Outside Cases	Total Autopsies
	Patients			Stillbirths					
	Priv.	Staff	Total	Priv.	Staff	Total			
Deaths	448	600	1108	34	14	48	1156		
Referred to coroner	58	25	83				83		
Available for autopsy by hosp. pathologist	390	635	1025	34	14	48	1073		
Autopsies done by hosp. pathologist	116	473	589	3	9	12	601	37	638
Percentage	29.7	74.5	57.4	9	64	25	56		
1938									
Deaths	449	679	1128	32	10	42	1170		
Referred to coroner	49	29	78						
Available for autopsy by hosp. pathologist	400	650	1050	32	10	42	1092		
Autopsies done by hosp. pathologist	141	509	650	12	7	19	669	65	734
Percentage	35.2	76.8	62	37.5	70	45.2	61.3		1372

Table 1 shows a statistical summary of the deaths and autopsies at the Vancouver General Hospital during the years 1937 and 1938. It should be pointed out that an autopsy rate of 62 per cent of all deaths and 76 per cent for the charity patients represents an excellent showing in a large, general, non-teaching hospital.

In tables 2 to 5 there is a tabulation of the 42 cases, showing age, sex, heart weight and postmortem diagnosis arranged under the following four headings: rheumatic heart disease, luetic heart disease, arteriosclerotic heart disease, and nephritis. There were no instances in this series of acute or subacute endocarditis or of thyroid heart disease. The division into the four main headings was made on a clinical and on a pathological basis. The distinction between arteriosclerotic heart disease and nephritis was not always clear cut. The latter classification was used when the kidney lesion was considered the primary cause of death, and usually meant a chronic glomerulonephritis with or without nephrosclerosis. In many of those listed as arteriosclerotic heart disease there was a degree of nephrosclerosis sufficient to account for some of the hypertension and accompanying cardiac hypertrophy, but the heart disease was considered primary. In the rheumatic and luetic cases the differentiation was less difficult though even in these cases there were instances of overlapping, in which more than one type of heart disease was present. Undoubtedly there were among these cases instances of malignant hypertension which came to their deaths as a result of cardiac or cardiorenal damage.

TABLE II

Rheumatic Heart Disease—8

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
1	53M	890	Aortic and mitral stenosis.
9	50M	800	Aortic stenosis.
20	47F	1000	Adhesive pericarditis; chronic nephritis; (H).
21	28M	1000	Aortic regurgitation; mitral regurgitation; chronic pericarditis; (H).
23	48F	780	Mitral stenosis (H); coronary sclerosis; old infarct; cerebral infarcts.
30	42M	1000	Aortic stenosis.
32	53M	780	Aortic stenosis.
36	11M	800	Chronic myocarditis; no valvular disease; pericardial adhesions.
	Av.	881	(H) indicates a significant hypertension.

TABLE III

Luetic Heart Disease—7

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
2	62M	1000	Aortitis with regurgitation; coronary sclerosis.
3	42M	1750	Aortitis with regurgitation; subacute nephritis.
22	48F	840	Aortitis with regurgitation; (H); coronary orifices narrowed.
25	38M	950	Aortitis with regurgitation; coronary orifices narrowed.
28	43M	1020	Aortitis with regurgitation; (H); narrowed coronary orifice.
33	39M	1040	Aortitis with regurgitation; coronary orifices narrowed.
38	43M	780	Aortitis with regurgitation; right coronary occluded.
	Av.	1054	(H) indicates a significant hypertension.

TABLE IV

Arteriosclerotic Heart Disease—14

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
4	57M	850	Coronary sclerosis; mitral sclerosis; nephrosclerosis; old hemiplegia.
6	64M	860	Aortic stenosis; (H); coronary sclerosis; old infarct.
7	51M	1090	Aortic stenosis; luetic aortitis.
10	58M	800	Coronary sclerosis; (H); old infarct; few pericardial adhesions.
11	87M	750	Coronary sclerosis; (H); few pericardial adhesions.
14	56M	760	Generalized arteriosclerosis; (H); coronary sclerosis; nephrosclerosis.
15	52M	750	Coronary sclerosis with thrombosis.
16	67M	750	Coronary thrombosis; (H); chronic nephritis.
18	56M	750	Coronary sclerosis with thrombosis.
27	45M	780	Coronary thrombosis; old infarct; (H); mitral and aortic sclerosis.
37	60M	750	Coronary sclerosis with thrombosis; old infarct.
40	44M	930	Generalized arteriosclerosis; (H); hydronephrosis.
41	64M	840	Coronary sclerosis with thrombosis; old infarct; terminating pericarditis.
42	67M	750	Coronary sclerosis with thrombosis; (H); luetic aortitis; aortic sclerosis; cerebral infarct.
	Av.	815	(H) indicates a significant hypertension.

TABLE V

Nephritis—13

Serial No.	Age Sex	Ht. Wt.	Postmortem Diagnosis
5	68M	800	Chronic nephritis; and nephrosclerosis.
8	74M	770	Chronic nephritis; (H); coronary sclerosis.
12	74M	750	Chronic nephritis; (H); aortic sclerosis.
13	61M	810	Chronic nephritis; (H); chronic myocarditis.
17	68F	750	Chronic nephritis; luetic aortitis; no regurgitation.
19	88F	750	Chronic nephritis; (H); chronic myocarditis.
24	70M	900	Chronic nephritis; generalized arteriosclerosis.
26	68M	810	Chronic nephritis; coronary sclerosis; (H).
29	88M	780	Chronic nephritis; mitral and aortic sclerosis; coronary sclerosis.
31	57F	900	Chronic nephritis; (H); generalized arteriosclerosis.
34	73M	780	Chronic nephritis; (H); aortic sclerosis; coronary sclerosis.
35	75M	780	Chronic nephritis; (H); generalized arteriosclerosis.
39	54M	1050	Chronic nephritis with acute exacerbation; (H).
	Av.	817	(H) indicates a significant hypertension.

The four types of heart disease show some difference in the average weight of these hypertrophied hearts:

Rheumatic	8 cases	881 grams
Luetic	7 "	1054 "
Arteriosclerotic	14 "	815 "
Nephritic	13 "	817 "

It would seem significant that the heart weight in the luetic group averaged about 200 grams more than in the other groups. One reason for this

may be that aortic lesions obviously add greatly to the work of the heart, especially the left ventricle, and in the main the coronary arteries are relatively free from sclerosis in this group. Thus, with tremendous increase in the demands on the heart muscle and in the presence of an adequate blood supply the greatest hypertrophy occurs. The narrowing of the orifices of one or both of the coronary arteries is probably a late development in the course of luetic aortitis.

Presented in tabular form the etiologic basis for the hypertrophy was as follows:

Rheumatic		
Chronic adhesive pericarditis	1	
Chronic myocarditis	1	
Valvular disease	6	
Aortic	5	
Mitral	1	8
Luetic		
Aortitis		
All with regurgitation		7
Arteriosclerotic		
Aortic stenosis	2	
Coronary sclerosis	10	
With thrombosis	8	
Generalized arteriosclerosis and hypertension	2	14
Nephritis (hypertension)		13
		42

These cases can be rearranged according to the structural or anatomic causes for the hypertrophy as follows:

Valvular defect			15
Aortic			
Stenosis	R.4	A.2	6
Regurgitation	R.1	L.7	8
Mitral			
Stenosis (with hypertension)			1
Pericarditis (with nephritis)			1
Myocardial involvement			13
Rheumatic			1
Coronary sclerosis			10
Coronary thrombosis			8
Generalized arteriosclerosis and hypertension			2
Nephritis			13
			42

The earlier teaching [4] as to the cause of cardiac hypertrophy indicated that aortic stenosis and adhesive pericarditis were common. In this series there were only six instances of aortic stenosis and only one of adhesive pericarditis. In the latter case an accompanying chronic nephritis undoubtedly accounted for some part of the hypertrophy. These findings would confirm the present view that adhesive pericarditis is of itself rarely, if ever, a cause of hypertrophy, and where the combination is found the cardiac enlargement is due to some accompanying cardiac abnormalities.[2]

The distribution of these hearts according to weight (free of clot) was as follows:

Over 1000 grams	5
1750–1090–1050–1040–1020	
901–1000 grams	
1000–1000–1000–1000–950–930	6
801–900 grams	9
750–800 grams	22
	42

The largest heart in this series, 1750 grams, occurred in a case of luetic aortitis with free aortic regurgitation, a subacute nephritis and moderate hypertension. The patient died of a lobar pneumonia. There were nine hearts weighing 1000 grams or more. It is generally agreed that when the heart weight exceeds 0.5 per cent of the body weight hypertrophy is present. In this series accurate body weights were not available in every case. In 10 patients in whom body weight (free of edema) had been recorded, the heart weight percentage (table 6) showed a variation from 0.93 to 1.8 in the adults. The one child in this series showed a heart equal to 2.6 per cent of his body weight. Table 6 shows that most of the adult cases were twice the upper limit of normal heart size and that four were three times that amount.

TABLE VI

Percentage Heart Weight of Body Weight

No.	Body Wt. Lbs.	Ht. Wt. Grams	%
36	67½	800	2.6
21	122	1000	1.8
25	139½	950	1.5
34	112	780	1.5
39	148	1050	1.5
23	145	780	1.2
37	135	750	1.2
38	143	780	1.1
42	180	750	1.0
27	184	780	0.93

NORMAL	Men	0.43
	Women	0.40
HYPERTROPHY OVER		0.50

CLINICAL ANALYSIS

The age in this group varied from 11 to 88, with 28 of the 42 cases past 50 years of age.

The sex distribution is of some interest, as of the 42 cases 36 were men and 6 women. Since hypertension and rheumatic heart disease both contribute to this series, and both show a preponderance of females, the large percentage of males in our series is not easily understood. The proportion of males to females is similar to that found in the clinical groups of arteriosclerotic heart disease and luetic heart disease in our hospital.

In reviewing the clinical records we were impressed by the short history given by many of these patients. It was not unusual for them to give a history of only a few weeks' or even only a few days' duration of the symptoms of congestive heart failure, dyspnea, weakness, and dropsy. In a few instances the patient was brought into the hospital for other than cardiac symptoms, as, for example, case 34 was brought in with ruptured gastric ulcer and case 11 with a primary carcinoma of the lung. In spite of this short history we hold the belief that the hypertrophy observed was a long time, months or even years, in developing. In this connection it is interesting to note that hypertrophy can develop in a very short time. J. M., a man aged 22 (not included in this series), became ill with an acute febrile illness, with pain in chest and cough, on October 7. On October 14, when he first consulted his doctor, a roentgen-ray showed a heart of normal size. One week later, October 21, a roentgen-ray showed tremendous enlargement of the heart shadow, which was then considered to be due to cardiac dilatation accompanying the acute aortic endocarditis that had developed. He died on November 7, one month after the onset of the illness and three weeks after a roentgen-ray showing a normal heart shadow. At autopsy, which showed an acute aortic endocarditis, his heart was greatly hypertrophied, weighing 950 grams. The rate of hypertrophy must vary considerably and was probably more than usually rapid in this case because of the youth of the patient. Palmer [10] mentions an instance of rapid hypertrophy in a girl of 12 with nephritis and hypertension in which a considerable increase of the heart shadow occurred in six months.

Physical signs of congestive failure were the rule, and in 35 of the 42 cases some degree of chronic congestion was present. These signs were tabulated as: (1) congestion of the lung bases; (2) peripheral edema; (3) enlargement of the liver; and (4) abnormal distention of the neck veins. In nine cases all four were noted; in 22 some combination of two or more of the four was present; in four only basal pulmonary congestion was found; and in seven there were no such signs present.

The blood pressure was recorded in 41 cases. It was classified as elevated if recorded as over 160 systolic or over 100 diastolic. It was elevated in 23 cases, below normal in two, and within normal limits in 16. From indications secured from the history and other examinations, such as the eyegrounds, it is our opinion that many of these patients had shown an elevated blood pressure previously.

Clinical signs of cardiac enlargement were noted in 35 of the 38 cases in which some record of this finding was made. For the purposes of this tabulation the grade of enlargement was classified according to the location of the left border as follows:

1. At midclavicular line ..... 13 cases
2. Outside midclavicular line ..... 5 "
3. In anterior axillary line ..... 10 "
4. In axilla ..... 7 "

Seventeen of the patients showed hearts enlarged to grades 3 and 4. It was surprising that, in view of the tremendous hypertrophy present, the clinical evidence of enlargement should not have been even more obvious. Roentgen-ray examination of the heart was carried out in 19 instances and in all revealed great enlargement.

Urinalysis revealed the expected findings in congestive failure. No renal function studies were carried out in these patients except the estimation of non-protein nitrogen in the blood which was increased in the nephritic group. No significant information was secured from the blood counts or the sedimentation rates performed on these patients.

Blood Kahn tests, done in 27 cases, were positive in seven and negative in 20. In the remaining 15 no report was available. Of the seven showing a positive Kahn, five had aortitis with regurgitation as the primary cause of the cardiac hypertrophy, and the other two showed aortic stenosis and cor-

TABLE VII

Analysis of Electrocardiograms

Case No.	Rhythm	Axis Dev.	R or S − T	T_1	T_2	T_3	B.P.	Coronary [1] Arteries	Type [2] H.D.
1	F	R	N	U	I	I	O	1	R
2	R	O	1 and 2 low	I	I	F	O	3	L
3	R	L	1 and 2 low	I	I	U	O	N	L
4	R	O	N	I	I	F	O	2	A
7	R	L	1 and 2 low	I	I	U	O	1	A
9	R	L	1 and 2 low	I	F	U	O	1	R
10	R	L	1 low	I	U	U	H	3	A
13	F	O	N	I	I	F	H	2	N
14	R	L	N	U	U	F	H	2	A
15	R	O	N	F	F	I	O	4	A
16	R	L	N	U*	U	U	H	4	A
17	R	L	1 low	I	U	U	O	N	N
20	R	L	1 and 2 low	I	I	U	H	2	R
21	R	L	1 and 2 low	I	I	U	H	N	R
22	R	L	1 low 3 high	I	I	U	H	N.O.	L
23	F	R	N	F	I	I	H	2	R
24	F	L	N	I	F	F	N	2	N
25	R	L	1 low	N	N	N	H	N.O.	L
27	R	L	1 low	I	I	U	H	4	A
28	R	B.B.	1 high 2 and 3 low	U	I	I	H	N.O.	L
29	H.B.	L	2 low	I	U	U	O	2	N
35	F	O	1 and 2 low	I	I	F	H	2	N
37	R	L	1 and 2 low	I	I	U	O	4	A
38	R	O	2 slurred	F	F	U	O	N.O.	L
40	R	L	1 and 2 low	I	U	U	H	2	A
42	R	L	1 and 2 low 3 high	I	I	U	H	4	A

1. Graded as follows:
   1. Beading.
   2. Sclerosis.
   3. Stenosis.
   4. Thrombosis.
   N.O.—Narrowed orifice.

2. R—Rheumatic.
   L—Luetic.
   A—Arteriosclerotic.
   N—Nephritic.

onary sclerosis respectively as the primary cause, with an aortitis as an accompanying finding. Among those with negative Kahn tests there were two with luetic aortitis found at autopsy. One of these cases, number 25, a man aged 38, with no rheumatic history showed a Corrigan pulse, a blood pressure of 120 systolic and 20 diastolic to 160 systolic and 70 diastolic, and a systolic and diastolic murmur at the aortic area. His blood Kahn was negative on two occasions. The other case, number 17, a woman aged 68, was diagnosed as chronic myocardial degeneration and chronic nephritis, and at autopsy was found to have in addition a luetic aortitis. In one additional case, number 33, a clinical diagnosis and the pathological finding of luetic aortitis were noted, but no record of a blood Kahn was found.

Electrocardiograms were obtained in 26 of the 42 cases at intervals of a few days to several months before death. In none of these was a normal tracing found. The pertinent electrocardiographic findings are tabulated in table 7 along with the blood pressure, condition of the coronary arteries, and the postmortem diagnosis. The commonest form of tracing was one showing a left axis deviation with a depressed R–T segment in the first lead and an inverted T_1 and T_2 and upright T_3. The rhythm was usually regular. Only five of these cases showed an auricular fibrillation, and one a partial heart block. Left axis deviation was the rule, but in six cases there was no abnormal deviation; in two it was to the right; and in one a branch block was present. The R–T or S–T segment was usually abnormal, the level of this segment in the first or second lead being below the iso-electric line in 18 of the 26 cases. It was in T-wave changes that the most consistent deviation from the normal was noted. The changes found were classified as follows:

Normal	3	(In one case T_1 was definitely flattened).
T_1 upright T_2 and T_3 inverted	3	
T_1 inv. T_2 and T_3 flat or upright	7	
T_1 and T_2 inv. T_3 flat or upright	13	

In 20 of the 26 cases, therefore, the T-wave was definitely abnormal and was of the type usually associated with the myocardial changes that result from deficient coronary blood flow, usually due to coronary sclerosis, but also due to narrowing of one or both coronary orifices by aortic valvular disease or aortitis. The blood pressure was normal in 12 and elevated in 14 of these cases, although as previously mentioned it is our impression that many had had a previous hypertension. The presence or absence of hypertension bore no relation to the electrocardiographic changes as listed, and this would seem to confirm the observation made by one of us (G. F. S.) [11] that cardiographic changes of this sort are due to coronary artery disease and the associated myocardial involvement rather than to hypertension per se.

The coronary arteries showed some evidence of abnormality in 23 of the 26 cases, i.e., a beading in three, a diffuse sclerosis in nine, a stenosis in two, a thrombosis in five, and narrowing of a coronary orifice in four. The normal coronary arteries were noted in one rheumatic, one nephritic, and one

luetic case, in each of which the cardiogram was abnormal, and in two of which the blood pressure was normal. The massive hypertrophy would of itself account for some of the electrocardiographic change.

Pathological Findings

The enlargement found was, in practically every case, a general hypertrophy and dilatation. The walls of both the left and right ventricle were greatly thickened. No evidence of enlargement of any one chamber, or of the inflow or outflow hypertrophy of Parkinson [2] was noted. This was not surprising inasmuch as these cases represented an extreme degree of cardiac enlargement past the stage of localized hypertrophy. Microscopically the heart fibers were enlarged. It was not true that the largest fibers were found in the largest heart, case 3, in which the heart weight was 1750 grams. The amount of myocardial degeneration and fibrosis showed considerable variation and raised the question as to the relative importance of true muscular hypertrophy and fibrosis as the cause for the increased heart weight. In most instances, of course, both enlargement of the individual muscle fibers and fibrosis were present. The weight as recorded was, of course, the weight of the heart alone free of blood and blood clot. In the tabulation tables 2 to 5 only the important cardiac postmortem findings are listed; and the rule was that most hearts showed overlapping, with two or more factors present to account for the hypertrophy.

The condition of the coronary arteries was carefully noted in every case, and in only seven of the 42 were they found to be normal. In these cases other obvious causes for hypertrophy were present. The coronary arteries in the remaining 35 cases were described as: beading or scattered plaques, 5; diffuse sclerosis, 13; stenosis, 4; thrombosis, 8; narrowed orifice (luetic aortitis), 5.

The liver showed chronic passive congestion in every case. In one instance, number 29, there was in addition a portal cirrhosis. The kidney findings have already been mentioned, the commonest lesion found being a chronic glomerulonephritis with an accompanying nephrosclerosis of varying degree in some cases.

There were in certain instances autopsy findings in addition to the cardio-renal damage sufficient to be a factor in causing death. Some of these have already been mentioned. They were a lobar pneumonia in number 3, bronchogenic carcinoma in number 11, enlarged prostate in number 24, cirrhosis of the liver, enlarged prostate and pulmonary abscess in number 29, perforated gastric ulcer in number 24, terminal hemorrhagic pancreatitis in number 35, hydronephrosis due to aberrant artery in number 40. In the remaining 35 cases the death was due solely to the cardio-renal-vascular changes.

The high incidence of coronary artery involvement in this series of enlarged hearts is in keeping with the observation of Palmer [10] that coronary

sclerosis per se is an important factor in the production of hypertrophy. He reports five cases with coronary sclerosis followed over one to four years, during all of which time the blood pressure remained normal, that showed progressive enlargement. Where, as is usual, the coronary sclerosis is associated with a hypertension the resulting hypertrophy is much greater. This relation of coronary sclerosis to the production of hypertrophy has some bearing on this present series. In the past the infectious types of heart disease, rheumatic or luetic, were considered the most likely causes of great enlargement. In recent years the importance of the degenerative changes associated with coronary sclerosis and hypertension has received more recognition. In this group it seems significant that only 15 of the 42 were due to the infectious type of heart disease, whereas 27 were due to degenerative changes. This present series may be affected to a certain extent by the fact that we have in this area, as has been reported for the Northwestern States,[12] a low incidence of rheumatic infection. In New England the incidence of rheumatic infection and, therefore, of the percentage incidence of rheumatic heart disease would be much greater.

Summary

Forty-two cases of cardiac hypertrophy of sufficient degree to be called true instances of *corda bovina* were collected from the autopsy material of the Vancouver General Hospital in 1937 and 1938.

These cases were all of approximately twice the upper limit of normal heart weight and they illustrate the importance of heart strain, work hypertrophy, in the production of cardiac enlargement.

Hypertension was probably the important clinical factor in producing this hypertrophy.

Chronic adhesive pericarditis was notable because of its infrequency.

Of the valvular lesions the aortic were commonest.

Coronary sclerosis was the important pathological finding and this combined with the hypertension produced the great enlargement.

The infectious types of heart disease accounted for only 15 cases, whereas the degenerative, arteriosclerotic changes accounted for 27.

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FELTY'S SYNDROME; ITS SEVERAL FEATURES, INCLUDING TISSUE CHANGES, COMPARED WITH OTHER FORMS OF RHEUMATOID ARTHRITIS *

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In 1924 Felty [1] described a syndrome occurring in five cases characterized by chronic rheumatoid arthritis, splenomegaly, and leukopenia. The syndrome occurred in individuals of middle age; all patients gave a history of marked loss of weight and all were undernourished; the arthritic process was distinctly chronic with an average duration of four and one-half years; the onset was either acute or gradual; and in the extremities occurred a generalized articular aching, which was mild but persistent, and accentuated by an occasional acute exacerbation.

In two of the cases the spleens were palpable just below the costal margins, in two others at the level of the umbilicus, and in the fifth case at a point five centimeters below the umbilicus. The spleens were firm, but not tender. No abnormality in the size or consistency of the livers was noted. In two cases the lymph glands were not enlarged, but in the other three the axillary, inguinal and epitrochlear nodes showed definite enlargement.

In four of the cases there was a slight secondary anemia, the red cells varying from 3.75 million to 4.80 million, and the hemoglobin from 70 per cent to 80 per cent. The color index averaged 0.85. Felty described a striking leukopenia, varying from 1000 to 4200 white blood cells, which he felt was a distinctive feature in every case. The differential formulae were not characteristic and eosinophilia was not present. The urines were normal with the exception of one case in which a urobilinuria was present. Stool examinations were negative. None of the patients showed any evidence of lues either serologically or on general examination. Three patients were afebrile during their hospital stay; two ran a low fever which subsided after one or two weeks.

In discussing this syndrome Felty advanced two likely explanations for it: (1) " The several features are manifestations of one pathological process, caused by a noxa which simultaneously affects the joints, the spleen, and the blood leukocytes. (2) The syndrome is merely the confusion of two separate clinical entities occurring coincidentally in the same individual. Taken separately without regard to the arthritis, the enlarged spleen with leukopenia and slight secondary anemia, the slight pigmentation of the skin, and the presence in the urine of urobilin, in the one case in which this was

* Received for publication December 7, 1938.
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sought for, are typical features of early Banti's disease." Felty concludes by stating that "one is more or less forced to the conclusion that this syndrome is a distinct clinical entity of which the outstanding symptoms are those related to the joints and the outstanding signs are the enlarged spleen and the blood picture."

Since the original report by Felty,[1] Hanrahan and Miller (1932),[2] Singer (1933),[3] Alessandrini (1934),[4] Craven (1934),[5] Price and Schoenfeld (1934),[6] Fitz (1935),[7] Singer and Levy (1936),[8] Williams (1936),[9] Reich (1936) [10] have described other patients with a syndrome of rheumatoid arthritis, an enlarged spleen, adenopathy, pigmentation of the skin, secondary anemia and leukopenia. Some of these observers have considered such a syndrome a definite clinical entity. Others have believed the "Felty syndrome" to be an uncommon but not unexpected manifestation of chronic rheumatoid arthritis. Still others have looked upon the syndrome as an end result of long standing infection.

Problem

Rheumatoid arthritis has long been considered a disease resulting from a source of infection which does not have its primary location in the joint. Hench [11, 21] has repeatedly emphasized that although the joints may be the most evidently diseased structures in rheumatoid arthritis, the course of the disease, its systemic manifestations and the pathological changes found in other tissues clearly demonstrate that the disease is a generalized one. Furthermore, if rheumatoid arthritis is a generalized disease, in some cases at least it would be expected grossly to involve other tissues such as the skin, muscle, spleen, liver, lymph glands and bone marrow. Many cases have been reported showing several of these systemic abnormalities. Little attention has been focused on the skin, muscle and vascular changes associated with rheumatoid arthritis.

With the belief that a pathological study of the skin, muscles and small blood vessels removed from an area unrelated to an involved joint in patients with rheumatoid arthritis might give further evidence whether or not the disease process was a generalized one, and also might aid in determining whether Felty's syndrome was a clinical entity or just an expected complex of the disease, we obtained such an examination on a group of 11 arthritics at the University Hospital. Four cases making up Group I (numbers 1, 2, 3 and 4) presented the entire syndrome described by Felty, that is, rheumatoid arthritis, leukopenia, enlarged spleen, anemia, and adenopathy. Three patients had biopsies of the skin and muscle. The fourth had a lymph gland biopsy. Four cases making up Group II (numbers 5, 6, 7 and 8) were selected as a measure of control, since they presented, in addition to rheumatoid arthritis and an enlarged spleen, a leukocytosis instead of leukopenia. Four cases making up Group III (numbers 9, 10, 11 and 12) were selected since they presented rheumatoid arthritis without either a palpable spleen or a leukopenia.

A brief summary of these cases together with their biopsy findings is as follows:

GROUP I

FELTY'S SYNDROME

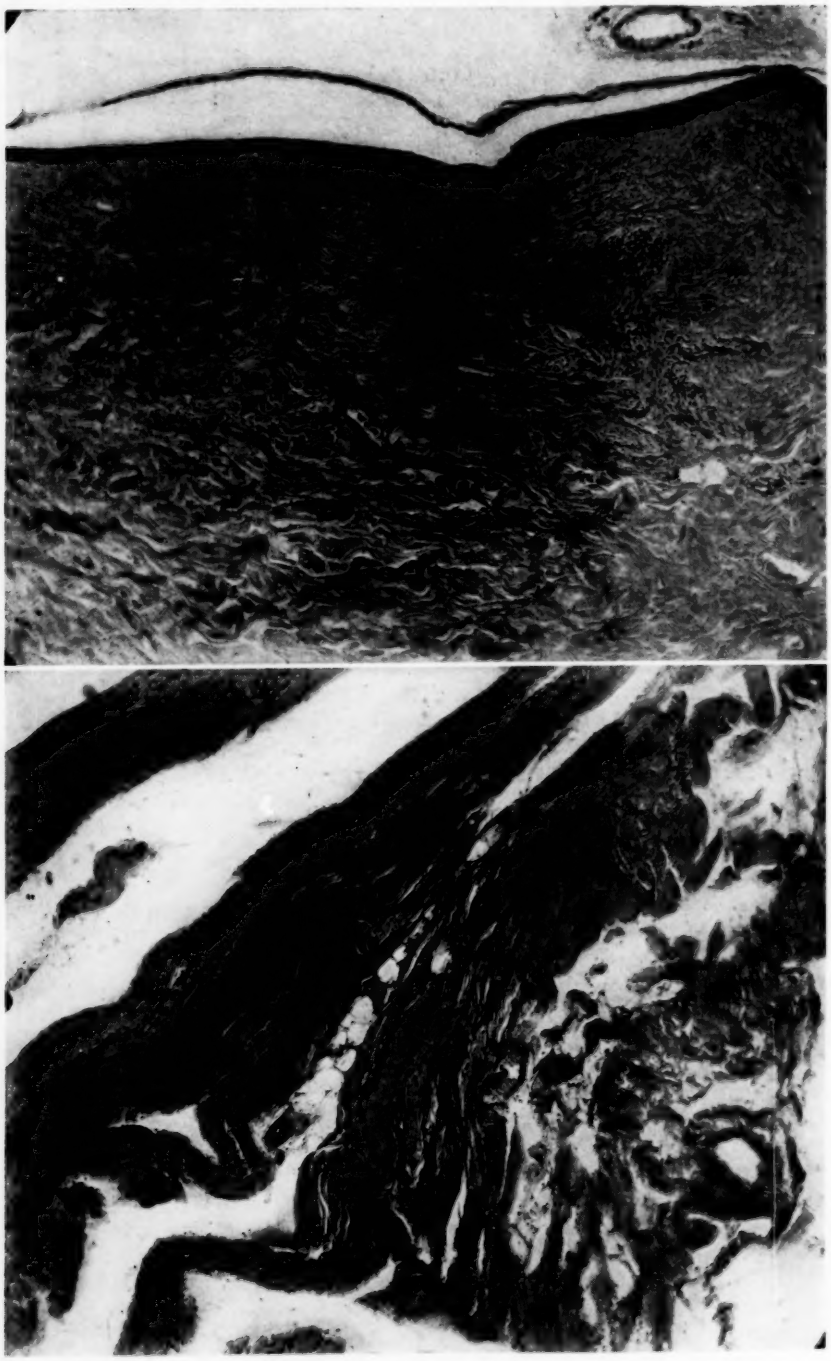
Rheumatoid Arthritis, with Leukopenia, Splenomegaly, Anemia and Adenopathy

Case 1. A white male (B. R.), aged 67, was admitted to the University Hospital July 27, 1934, complaining of pain and stiffness in his joints of seven years' duration. Four to five months prior to admission the joint involvement had become worse with increasing stiffness and loss of motion. There had been a chronic cough for two to three years, productive of two to three tablespoonsful of yellow sputum daily. There had been a loss of 25 pounds of weight since 1933. His past history was unessential with the exception of a nocturia of one to three times which he had had for a number of years.

Examination: Showed a pale, undernourished, asthenic-appearing white adult male. There was fusiform swelling of the wrists and interphalangeal joints of the hands, with limitation of motion in the hands, wrists, elbows, shoulders and cervical spine. There were bean-sized lymph glands in the inguinal and epitrochlear regions. The lungs showed a few fine post-tussive râles at the right apex anteriorly below the clavicle. In the abdomen the liver border was palpable one finger's breadth below the costal margin on deep inspiration. The spleen was also "palpable." Otherwise the physical examination was not significant.

Laboratory findings: Several urine examinations were negative. The blood examination on admission showed a 55 per cent hemoglobin, 4,300,000 red blood cells, 2,850 white blood cells. The differential smear showed the polymorphonuclears to be 45 per cent, basophiles 1 per cent, eosinophiles 1 per cent, lymphocytes 45 per cent, mononuclears 8 per cent. The red blood cells showed moderate acromia with no change in their size or shape. Platelets were normal in number. Numerous subsequent blood examinations were made, and on iron therapy the hemoglobin rose from 52 per cent to 74 per cent at the time of discharge. There was also a gradual increase in the red blood cell count up to 5.2 million at the time of discharge. The white blood cells varied, ranging from 2,700 to 4,200. The routine stool examination was negative. Routine blood Kahn test was negative. Basal metabolic rate was —5 per cent. A biopsy of the calf muscles on August 9, 1934 showed a marked fibrosis of the corium (see figure 1). In the adipose tissue were small blood vessels which showed practically complete obliteration, as well as several with active inflammation. The muscle showed a localized increase in interstitial nuclei with small perivascular infiltrations (see figure 1 A). A roentgen-ray examination of the left shoulder, right wrist and hand showed osteoporosis and irregularity of the lateral and medial margins of the first phalanges of the right hand, probably due to arthritis. A stereoscopic projection of the thorax showed a minimal parenchymal lesion of the right apex evidently tuberculous in nature. The activity by roentgen-ray was indeterminate at that time. During the patient's hospitalization he had frequent elevations of temperature to 99.5° F. and above, and on one or two occasions to 101°. The pulse ranged from 70 to 108 per minute. All sputum examinations were negative for acid fast bacilli and it was concluded that the parenchymal lesion in his right apex was inactive. He was discharged on September 18, 1934.

He returned to the University Hospital on July 10, 1935, stating that his weakness, ease of fatigue and tiredness of the legs had increased, and that he had lost 10 more pounds in weight. A slight incontinence of urine had developed since his last admission.



FIGS. 1–1*A*.

The examination was essentially the same as before except that the prostate gland was hard, showed a two plus enlargement, and was quite nodular. The Department of Urology made a diagnosis of carcinoma of the prostate. Roentgen-ray reports showed no activity of the chest lesion. There was no evidence of metastatic carcinoma of the spine or pelvis. A blood count on readmission showed the following findings: Hemoglobin 68 per cent, red blood cells 4,120,000; white blood cells 2,500; polymorphonuclears 42 per cent, eosinophiles 1 per cent, lymphocytes 47 per cent, mononuclears 5 per cent, myelocytes 4 per cent, lymphoblasts 1 per cent. The patient was discharged on July 24, 1935 with the advice that he should return for a biopsy of his prostate, but unfortunately he did not return and no further information is available about him.

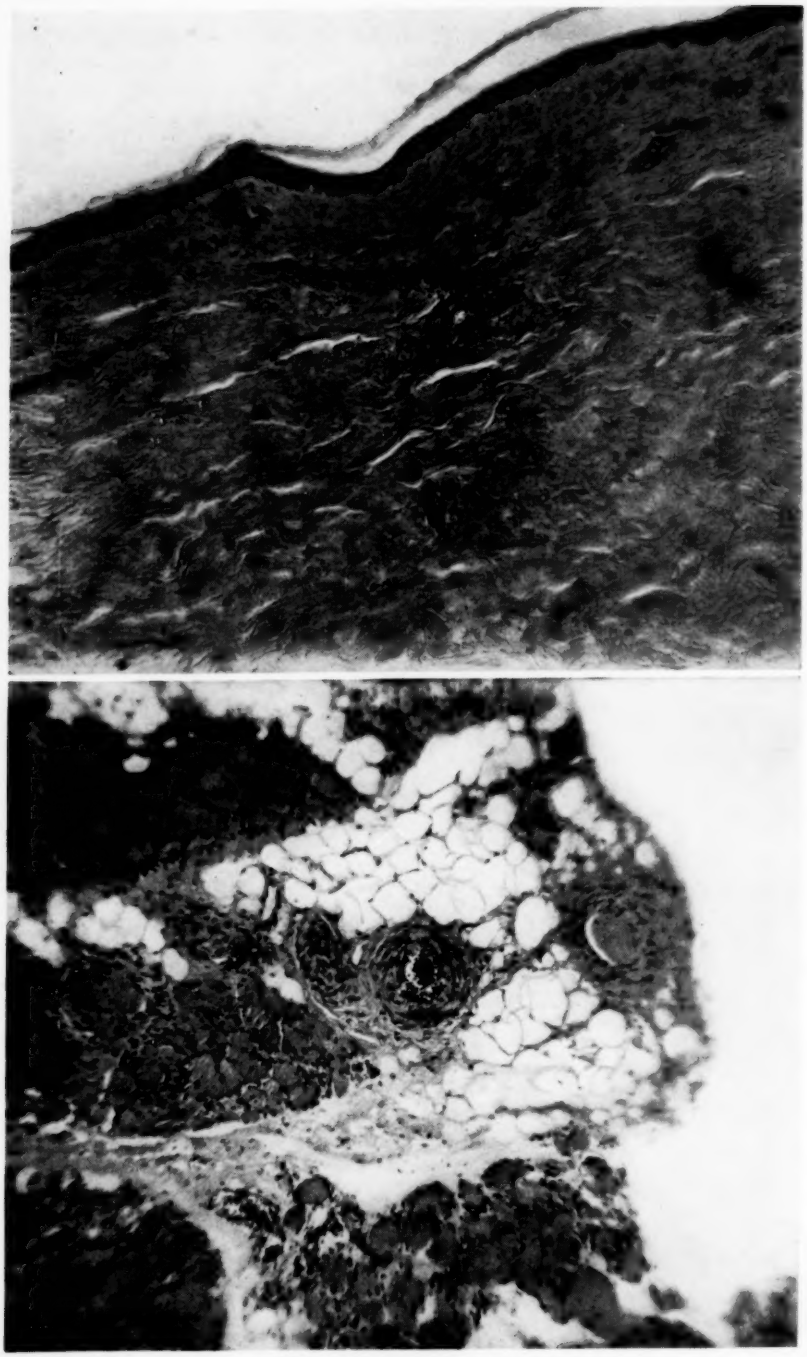
Case 2. A white male (L. M.), aged 47, was admitted to the University Hospital on August 20, 1934 complaining of weakness and stiffness of his joints. Three years prior to admission, the patient stated, he had a swelling the size of a walnut in the left side of his neck for a period of two weeks. The mass was not tender and finally broke inside followed by a severe fever. His weakness continued and he had been in bed continuously the year before admission. Also one year before admission he complained of joint symptoms, including swelling and redness beginning in the right hand and fingers and then the elbows, left hand, knees and ankles. A residual stiffness had remained in the ankles, knees and the last three fingers on the right hand. He had lost over 100 pounds during the previous three years. The past history was otherwise negative.

Examination: Showed a fairly well developed but markedly emaciated white adult male appearing chronically ill. The skin was dry and inelastic showing the evidence of marked weight loss. The mouth showed several teeth to be missing. The tonsils had been removed. The neck was negative except for small glands in the left posterior cervical chain. A few râles were heard at both lung bases posteriorly. Examination of the heart showed no enlargement. Examination of the abdomen showed the liver enlarged two fingers' breadth below the right costal margin. The spleen was felt three fingers' breadth below the left costal margin. The extremities presented typical fusiform swelling of the joints with marked emaciation and muscular atrophy. There was some limitation of motion in the joints, particularly in the latter three fingers of the right hand. The nails were rounded. There were small bilateral inguinal and axillary lymph glands and bilateral enlarged epitrochlear glands. Otherwise the physical examination was not significant.

Laboratory findings: The routine blood Kahn test and urine analysis were negative. Examination of the blood on August 20, 1934 showed hemoglobin 49 per cent, red blood cells 2.9 million, white blood cells 5,500 with 70 per cent polymorphonuclears, 19 per cent lymphocytes, 9 per cent monocytes, 2 per cent basophiles; the red blood cells appeared pale in color but were otherwise normal. On August 30, 1934 the hemoglobin was 55 per cent, the white blood cells, 11,000. On September 7, 1934 the hemoglobin was 43 per cent, red blood cells 2.19 million, white blood cells 5,100, with a differential count approximately as above. On September 13, 1934 the hemoglobin was 53 per cent, red blood cells 3.56 million, white blood cells 3,650; 78 per cent polymorphonuclears, 17 per cent lymphocytes, 3 per cent eosinophiles, 2 per cent basophiles. A calf muscle biopsy on August 24, 1934 showed slight atrophy of the skin. In the corium were occasional small perivascular infiltrations of lymphocytes, plasma cells and a few leukocytes (figure 2). The muscle showed atrophy, hypertrophy and variation in staining with an increase in the interstitial nuclei but no perivascular

FIG. 1. *Above* (Low power). Case 1. (B. R.) Age 67. Duration of arthritis 7 years. Loss of 25 pounds. Fusiform swelling of joints. Liver and spleen palpable. Hgb. 55 per cent; w.b.c. 2,850. The biopsy from the calf shows atrophy of epithelium, fibrosis of corium, and occasional small perivascular infiltrations in the corium.

FIG. 1 *A. Below* (Low power). Case 1. (B. R.) The voluntary muscle shows an increase in the interstitial nuclei and small perivascular infiltrations.



FIGS. 2–2*A*.

infiltration (figure 2A). Agglutination tests were negative for *B. typhosus, B. paratyphosis A* and *B, Br. abortus, Br. melitensis* and *Br. suis.* A stool culture showed no organisms of the typhoid dysentery group. Two blood cultures, one on admission and one shortly thereafter, were reported as negative. On September 19, 1934 a stereoscopic roentgen-ray of the chest was negative for parenchymal disease.

The patient had a persistent fever throughout his course in the hospital, varying from 99 to 101° F. daily. He was discharged September 21, 1934.

Case 3. A white female (B. T.), aged 34, entered the University Hospital April 6, 1935 complaining of rheumatism of six years' duration. She had been practically an invalid for two years previous to her admission. There had been a weight loss of 30 pounds in the six year period. The past history was uneventful.

Physical examination: Revealed a slender, undernourished, adult female. Her mouth was edentulous, her tonsils were absent, and her lung fields were clear. The joints presented typical fusiform swelling. There was ulnar deviation and some abduction of the right hand and a flexion deformity of both elbows. The spleen was palpable but the liver was not felt. There was flexion deformity of both knees with swelling and pain on motion. The ankles showed only stiffness.

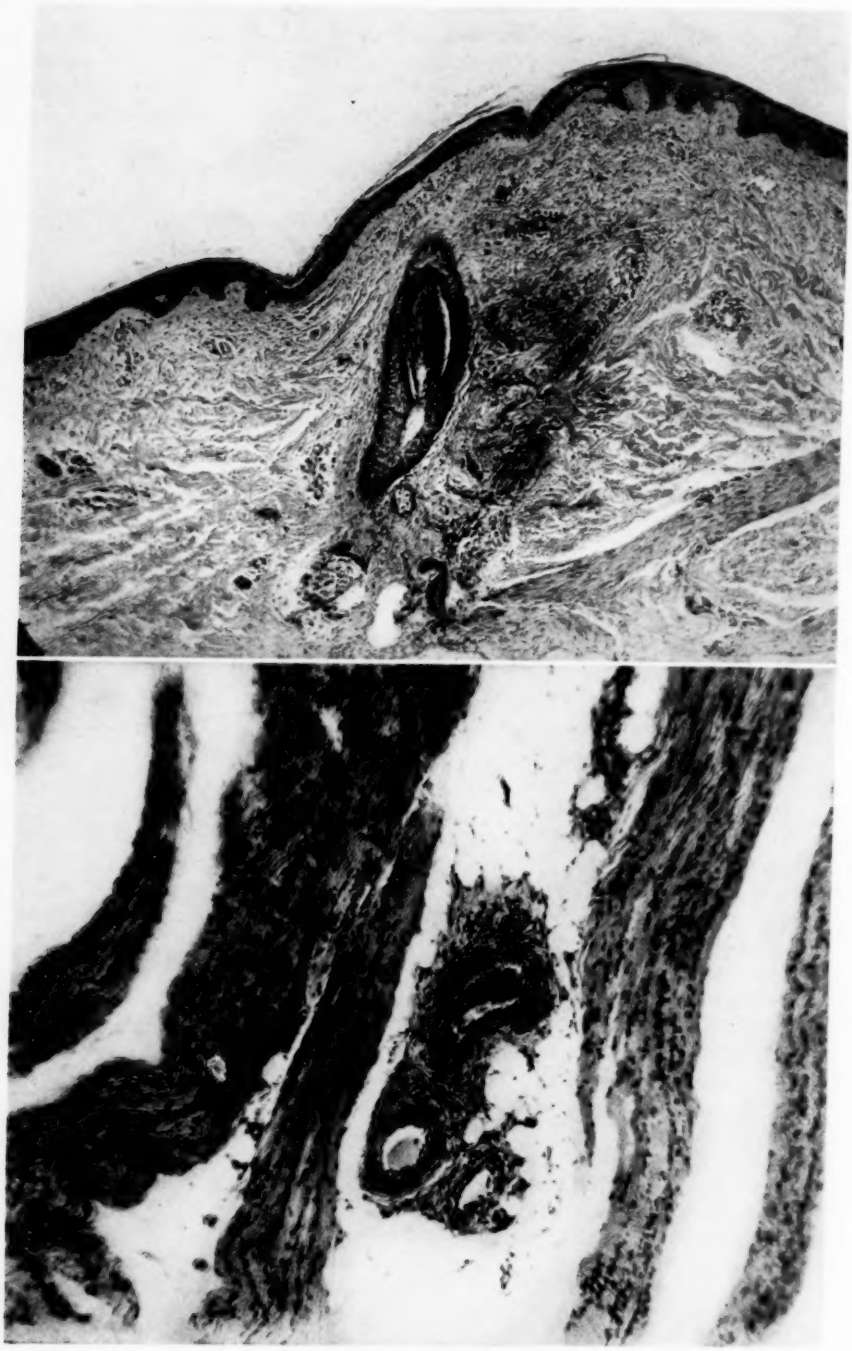
Laboratory findings: Routine blood Kahn test was negative, and several urinalyses were all negative. The blood count on April 7, 1935 showed a hemoglobin of 58 per cent, 3,750,000 red blood cells, 3,100 white blood cells. The differential count showed 60 per cent polymorphonuclear cells, no basophiles, no eosinophiles and 40 per cent lymphocytes. No monocytes were present. Roentgen-rays of both knees on April 8, 1935 showed advanced atrophic arthritis with beginning erosion of the articulating surfaces of both knees, and beginning subluxation.

This patient's temperature varied from 99.5 to 101° F. for the first seven weeks that she was in the hospital. About May 25, 1935 her temperature gradually began to increase up to 102° F. daily, and on June 20, 1935 her temperature went to 104° F. This remained septic in type, daily reaching from 103 to 104° F. On June 11, 1935 a biopsy of the calf muscle was obtained which showed an atrophy of the epidermis and a number of small perivascular inflammatory foci in the dermis (figure 3). The muscle showed well marked changes with simple and fatty atrophy and small perivascular inflammatory foci, chiefly lymphocytic. A blood culture was taken on June 20, 1935, which was reported as showing *Staphylococcus aureus.* It was concluded, therefore, that some time about May 25, 1935 this patient had developed a septicemia. Her condition grew progressively worse and on July 1, 1935 her respirations ceased.

At autopsy the liver and spleen were both markedly enlarged. All muscles, including the heart muscle, were markedly atrophic. There was an acute abscess anterior to the vertebral column and posterior to the larynx, as well as a small abscess in the left lung. On microscopic section of the spleen, the following report was made: "Acute exacerbation of chronic passive congestion. Hyaline material, apparently amyloid, in many of the follicles. Numerous bone marrow giant cells in the sinusoidal spaces." All lymph nodes showed a chronic type of lymphadenitis with marked hyperplasia of the sinus reticulum. After decalcification, the sternum, vertebral body, and ribs showed a congestive marrow which was 90 per cent cellular. In one of the long bones there was fatty marrow associated with osteoporosis. The bone marrow from the femur was about 50 per cent cellular. Sections from the muscles of the thorax and back showed perivascular lymphocytic infiltration.

FIG. 2. *Above* (Low power). Case 2. (L. M.) Age 47. Duration of arthritis one year. Weight loss of 100 pounds. Fusiform swelling of joints. Liver and spleen palpable. Anemia and leukopenia. The calf biopsy shows atrophy of the skin with occasional small perivascular infiltrations of lymphocytes, plasma cells and a few leukocytes.

FIG. 2*A*. *Below* (Low power). Case 2. (L. M.) The muscle fibers show simple and fatty atrophy, hypertrophy, variation in staining and an increase in the interstitial nuclei. No perivascular infiltrations are present.



FIGS. 3–4.

Case 4. A white male (B.S), aged 64, was admitted to the University Hospital on August 3, 1937, with the chief complaint of rheumatism of nine years' duration. At the onset, he had noticed painful feet with swelling which lasted from three to four weeks. Since then, he had had recurrent attacks yearly, usually in the summertime. The attack noted on admission had started six weeks prior to that date, at which time he first observed swelling and pain in the left wrist and hand with loss of motion and some redness, leaving pain in the right sacroiliac area, the right shoulder and neck. He had lost 55 pounds in weight during the past nine years' time. His history was otherwise uneventful.

Physical examination: The patient was obviously undernourished and was in some acute distress. His temperature was 100.5° F. The spleen was palpable two fingers' breadth below the left costal margin, and the liver was palpable three fingers' breadth below the right costal margin. The wrists were swollen, warm and tender, and painful on motion. There was slight pain on motion of the elbows, shoulders and knees, but no swelling, warmth or limitation of motion.

Laboratory findings: Various urine examinations were entirely negative. The blood count on August 7, 1937 showed 62 per cent hemoglobin, 4,300,000 red blood cells, 2,200 white blood cells. The smear showed 18 per cent polymorphonuclear neutrophiles, 70 per cent lymphocytes, and 4 per cent monocytes. The red blood cells were hypochromic, and the platelets were abundant. The white blood cell count on August 11, 1937 was 2,800. Stool examination was entirely negative, and blood agglutinations for *Brucella abortus, melitensis,* and *suis* were negative on August 9, 1937. The blood Kahn was negative. Chest roentgen-ray showed only pulmonary emphysema. A biopsy of a maxillary lymph node was obtained on August 17, 1937 which showed well-marked lymphoid hyperplasia. The follicular architecture was well preserved, suggesting that the process was apparently inflammatory. No biopsy of the skin or muscle was obtained.

Group II

Rheumatoid Arthritis with Splenomegaly but without Leukopenia

Case 5. A white male (W. T.), aged 27, was admitted to the University Hospital August 23, 1935 complaining of painful and swollen joints. Five years prior to admission he had an attack of influenza following which he developed a sharp pain beneath the right costal margin made much worse by deep breathing. Two months later he developed painful, red, swollen knee joints. Since that time all the joints of his body have become involved in a similar fashion. He had had a cough productive of about a quarter of a cupful of mucoid sputum daily which had occasionally been blood-tinged. He had lost a total of 40 pounds in weight during the past year. His past history was essentially negative.

On examination his temperature was 100, pulse was 130 and respirations were 30. The patient was an undernourished, white male lying in bed appearing chronically ill. The tonsils had been surgically removed. The lung fields were clear and the heart was negative. Blood pressure was 138 mm. of mercury systolic and 90 diastolic. In

FIG. 3. *Above* (Low power). Case 3. (B. T.). Age 34. Duration of arthritis 6 years. Thirty pounds weight loss. Fusiform swelling of joints. Palpable spleen. Anemia and leukopenia. The calf biopsy showed a number of small perivascular inflammatory foci of lymphocytes and polymorphonuclear leukocytes in the skin. Very slight atrophy of the skin is present.

FIG. 4. *Below* (Low power). Case 6. (M. P.) Age 44. Duration of arthritis 10 years. Weight loss of 40 pounds. Fusiform swelling of joints. Liver and spleen both palpable. Hgb. 54 per cent, W.B.C. 13,450. The calf biopsy shows atrophy of the muscles and marked increase in interstitial nuclei. Small perivascular infiltrations can be seen about some of the arterioles.

the abdomen the spleen was just barely palpable beneath the left costal margin. The liver was not felt. Rectal examination was negative. There was generalized pea to bean sized firm lymphadenopathy. The joints showed extensive fusiform swelling with multiple flexion deformities.

Laboratory findings: The routine blood Kahn test was negative. Urinalysis on three occasions showed 1 to 2 plus albumin, a negative test for sugar, specific gravity of 1.020. Microscopic examination of the sediment showed one to two red blood cells per high power field, an occasional white blood cell and a few granular casts. Blood studies on August 22, 1935 showed a hemoglobin of 48 per cent (Sahli), with 3.46 million red blood cells and 9,100 white blood cells per cubic mm., with 72 per cent polymorphonuclears, 3 per cent eosinophiles, 20 per cent lymphocytes and 2 per cent monocytes. After iron therapy and one blood transfusion the hemoglobin on October 2, 1935 was 77 per cent (Sahli) with 3.77 million red blood cells per cubic mm. Two stool examinations showed a negative guaiac test, and 1–3 plus benzidine test for occult blood. Two sputum examinations showed no acid fast organisms. The blood non-protein nitrogen was 18 mg. per 100 c.c. on August 24, 1935. Blood cultures taken on September 4, 1935 and September 19, 1935 were both negative. Agglutination tests reported on September 6, 1935 were negative for *B. typhosus, paratyphosus A* and *B., Br. abortus* and *Br. melitensis.* The patient was a type II in blood grouping. A throat culture showed *Streptococcus viridans, Streptococcus anhemolyticus, Hemophilus hemolyticus* and a large gram positive micrococcus. Concentrated sputum examination for acid-fast bacilli was negative. Electrocardiogram on September 6, 1935 was reported as not definitely abnormal. A calf muscle biopsy on September 17, 1935 showed the absence of any inflammatory infiltrations in the skin. There was no increase in interstitial nuclei and perivascular infiltration. No changes were present which suggested angiomyositis. Stereoscopic roentgen-rays of the chest on August 26, 1935 and September 6, 1935 showed a negative chest. Roentgen-rays of the right elbow, right hand and right knee showed atrophic changes of all these joints. Bronchographic studies after the injection of iodized oil on October 14, 1935 showed no evidence of gross abnormality of the bronchi and no signs of bronchiectasis.

Case 6. A white female (M. P.), aged 44, was admitted to the University Hospital May 30, 1934 complaining of stiffness and deformity of the joints. Ten years before the patient had experienced swelling, redness, tenderness, and limitation of motion in the joints. Her first symptoms began in the ankles and later involved the wrists, finger joints, elbows, shoulders, knees and hips. In the last eight years there had been a progressive deformity of the above mentioned joints. She had remained up and about, being able to do most of her housework until six months prior to admission. At that time she developed influenza following which her rheumatism became markedly exacerbated, and walking became more difficult and painful. She had lost 40 pounds of weight.

Physical examination: Showed an emaciated patient appearing older than her actual age. All teeth had been recently extracted, and the tonsils had been removed. No adenopathy was present. The lung fields were clear and the heart was normal in size. The blood pressure was 126 systolic and 88 diastolic. The liver border was palpable two cm. below the rib margin. The spleen was definitely enlarged and could be felt below the left rib margin. There was fusiform swelling of the interphalangeal joints of both hands, the wrists and the knees, with some limitation of motion.

Laboratory findings: The blood Kahn test and urine analysis were negative. A blood count showed 54 per cent hemoglobin, 4.09 million red blood cells, 13,450 white blood cells; the differential smear showed 79 per cent polymorphonuclears, 2 per cent basophiles, 1 per cent eosinophiles, 15 per cent lymphocytes and 3 per cent monocytes. The red blood cells showed moderate acromia, but were normal in size and shape. The platelets were normal. A stool examination showed 1 + benzidine on a meat con-

taining diet. Stereoscopic roentgen-ray of the chest was negative. A roentgen-ray examination of the left knee showed chronic atrophic arthritis with definite atrophy of the tissue above and below the joint. Demineralization of the bone was present and there was a mild loss in the joint space. A biopsy of a calf muscle was done on July 12, 1934 and repeated on September 11, 1934. The first biopsy showed slight maceration of the epidermis. The dermis and panniculus showed no lesion other than operative hemorrhage. The voluntary muscle was distinctly abnormal. It was atrophic and the interstitial nuclei were increased. Around some of the small arteries there was a slight inflammatory reaction. The second biopsy showed some atrophy of the voluntary muscles. The muscle fibers were in part atrophic and in part hypertrophic. A definite increase of interstitial nuclei was present. The blood vessels showed a perivascular infiltration in several instances (see figure 4).

On August 5, 1934 the patient was discharged.

She returned to the University Hospital on September 10, 1934 without much change in her symptoms. Examination showed that her physical signs were approximately the same as at the time of discharge. The blood examination on September 10, 1934 showed 66 per cent hemoglobin, 4.1 million red blood cells, 7,500 white blood cells, and a differential smear showed polymorphonuclears 70 per cent, eosinophiles 4 per cent, lymphocytes 20 per cent, monocytes 6 per cent. The smear showed acromia of the red cells but otherwise was normal. October 22 the hemoglobin was 53 per cent, white blood count 7,350. Stool examination was negative.

Case 7. A white female (J. K.), aged 58, was admitted to the University Hospital on June 11, 1934, and discharged June 28, 1934. Her chief complaint was that of painful, deformed joints which she had had for four years. At the onset of her disease, she had had tenderness, swelling and painful motion of multiple joints, which included the joints of the hands, feet, knees and right shoulder, all of which had rapidly increased in severity six months prior to admission.

Physical examination: This patient was distinctly undernourished. The skin showed numerous pigmented, slightly elevated nevi over the abdomen and evidence of slight pallor. The teeth had been extracted. The tonsils were atrophic. The spleen was definitely enlarged, extending three fingers' breadth below the left costal margin. The liver was palpable one finger's breadth below the right costal margin. There was marked limitation in range of motion in both shoulders, more marked on the right. There was fusiform swelling of the elbows and wrists with moderate flexion deformity of both and distinct ulnar deviation of the hands. The knees were slightly tender to palpation.

Laboratory findings: Routine blood Kahn examination was negative and several urine analyses were all negative. The blood count on admission showed 60 per cent hemoglobin, 4,470,000 red blood cells, 10,950 white blood cells, and the differential count showed 84 per cent polymorphonuclear neutrophiles, 1 per cent eosinophiles, 11 per cent lymphocytes, and 4 per cent monocytes. Stool examination was negative. A biopsy of the calf muscle was taken on September 6, 1934. There was both simple and fatty atrophy of the voluntary muscles. An active interstitial myositis was present with infiltrations around the small blood vessels and capillaries (figure 5). The arteries were of somewhat larger caliber and showed a definite periarteritis and angiomyositis. Roentgen-ray examinations of the bones of both hands showed chronic arthritis, of the mixed type, bilaterally. The carpal bones showed a fairly marked degree of calcium loss and apparent narrowing of interosseous joint spaces.

Case 8. A white male (F. K.), aged 56, was admitted to the University Hospital on November 28, 1934, and discharged on December 24, 1934. He gave a history of pain at various times for over a period of 18 years in different joints, including his hands, wrists, elbows, shoulders, knees, ankles, hips, back and neck. The initial attack was in the right hip. His condition had been progressively worse during the previous six years. For the six weeks prior to admission there had been some

swelling, soreness and pain in the right knee and hip, and he had been unable to walk for four weeks. He had lost a total of 12 pounds in the three months prior to admission. The history was otherwise uneventful.

Physical examination: This patient's weight was 110 pounds. Examination of the head and neck was negative. There was moderate submaxillary adenopathy bilaterally. No other enlarged lymph glands were noted. The spleen was palpable

FIG. 5. (Low power). Case 7. (J. K.) Age 58. Duration of arthritis four years. Fusiform joint swelling. Spleen enlarged three fingers' breadth. Anemia, leukocytosis. The biopsy from the calf showed simple and fatty atrophy of the voluntary muscle. An increase in the interstitial nuclei is present. Several perivascular infiltrations of lymphocytes and leukocytes can be seen.

two fingers' breadth below the left costal margin. The liver was not felt. There was marked fusiform swelling of knees, hands, wrists, and toes. Complete flexion of the fingers and wrists was impossible. The motion of the left elbow was restricted from 90 degrees to about 120 degrees. The physical examination otherwise was negative.

Laboratory findings: The routine blood Kahn test for syphilis was negative, and several urine examinations were entirely normal. A blood count on December 2, 1934 showed 78 per cent hemoglobin, 4,600,000 red blood cells, 9,600 white blood cells. The

smears showed 70 per cent polymorphonuclear neutrophiles, 2 per cent eosinophiles, 24 per cent lymphocytes and 3 per cent monocytes. A basal metabolic rate was + 10 per cent. A biopsy of the calf muscle was done on December 11, 1934 and showed an occasional slight perivascular increase in wandering cells and a slight increase of interstitial nuclei, with evidence of clumping. The small vessels showed no significant lesion. Roentgen-rays of the right knee and left elbow showed mixed arthritis with osteoporosis of the bones of these joints. There was a fair amount of periarticular swelling of the right knee joint. Bony articular cortex was thin, and there was slight hypertrophic lipping of the external condyle.

Group III

Rheumatoid Arthritis, without Leukopenia or Splenomegaly

Case 9. A white male (J. V. D.), aged 49, was admitted to the University Hospital on February 17, 1936 complaining of pain in his joints of 17 months' duration. The process had started in his ankles, but had within a few weeks involved the knee joints, right wrist, index and little fingers of the left hand, and all the fingers on the right hand. The left shoulder joint had also become painful, stiff and swollen. The process had been progressive up to the time of admission. He had lost 50 pounds of weight in the period since the onset of his illness. As a child, he had had measles, mumps, chicken-pox and whooping cough. There was no history of scarlet fever or rheumatic fever. He had had a tonsillectomy in January 1935, and all of his teeth had been extracted one year prior to admission.

Physical examination: Revealed an adult male who did not appear to be acutely ill. Examination of his head and neck was negative. The lung fields were clear and his heart was normal. The liver and spleen were not palpable. His knee joints, ankles, right wrist, and left index and little fingers presented the typical fusiform swelling of rheumatoid arthritis with stiffness. There was no redness present. The cervical, axillary, epitrochlear, and inguinal nodes were present but not enlarged or tender.

Laboratory findings: The routine blood Kahn test for syphilis was negative. Several urine examinations were entirely negative except for sugar, and the diagnosis of diabetes mellitus was eventually made. The blood count on February 18, 1936 showed 70 per cent hemoglobin, 4,190,000 red blood cells, 9,000 white blood cells; 50 per cent polymorphonuclear cells, no basophiles, 3 per cent eosinophiles, 45 per cent lymphocytes, and 2 per cent monocytes. A biopsy of the calf muscle obtained on February 25, 1936 showed very slight perivascular infiltration in the skin and no recognizable changes in the muscle. Stereoscopic roentgen-ray of the chest was entirely negative. No other roentgen-rays were obtained.

Case 10. A white female (M. R.), aged 47, was admitted to the University Hospital on January 31, 1936. Although her chief complaint was that of a vaginal tumor, she gave a history of having had "arthritis" since the age of four. This had become severe at the age of 14 following an attack of scarlet fever, and it was again accentuated following the delivery of her first child 13 years before admission. She had actually gained weight during the past three years. Pain and stiffness of her joints had been progressive during the previous 10 years.

Physical examination: Revealed submental, cervical, axillary, epitrochlear and inguinal gland enlargement. This was very mild, however. There was a cystic area present in the right breast. The extremities presented well marked fusiform swelling of the joints which involved the toes, fingers and hands primarily. However, the larger joints, such as the elbow, knee, shoulder, hip and ankle joints also showed some limitation of motion and pain. Pelvic examination was negative.

Laboratory findings: The routine Kahn test was negative. Repeated urine ex-

aminations were all normal. A blood count on January 31, 1936 showed 86 per cent hemoglobin, 9,500 white blood cells. On February 24, 1936 the hemoglobin was 75 per cent with 4,290,000 red blood cells, 5,750 white blood cells, 62 per cent polymorphonuclear leukocytes, no basophiles, 4 per cent eosinophiles, 20 per cent large lymphocytes, 6 per cent small lymphocytes, and 8 per cent monocytes. The red blood cells

FIG. 6. (Low power). Case 10. (M. R.). Female, age 47, admitted January 31, 1936. Duration of arthritis 25 years. No weight loss. Fusiform joint swelling. No anemia. W.B.C. 9,600. Spleen not palpable. The biopsy from the calf showed several small foci of perivascular infiltrations in the muscle which were chiefly lymphocytic.

appeared normal. Stool examination was entirely negative. Roentgen-ray examinations of the right knee and spine showed advanced atrophic arthritis in each knee with considerable hypertrophic spurring, more on the right than on the left. There was minimal osteoporosis of the spine. There was advanced atrophic arthritis of both hip joints. A biopsy of a calf muscle on February 27, 1936 showed small perivascular lymphocytic infiltration in the skin and several small foci of perivascular infiltration in the muscle, chiefly lymphocytic, characteristic of an angiomyositis (figure 6).

This patient had a dilatation and curettage on February 4, 1936 which showed only polypoid hyperplasia. A tumor of the left breast, removed on February 8, 1936, showed a papilliferous cystadenocarcinoma. The patient had only a simple mastectomy, and the postoperative course was uneventful.

Case 11. A white male (J. M.), aged 53, was admitted to the University Hospital on February 26, 1936, complaining of arthritis in the knees and feet of four

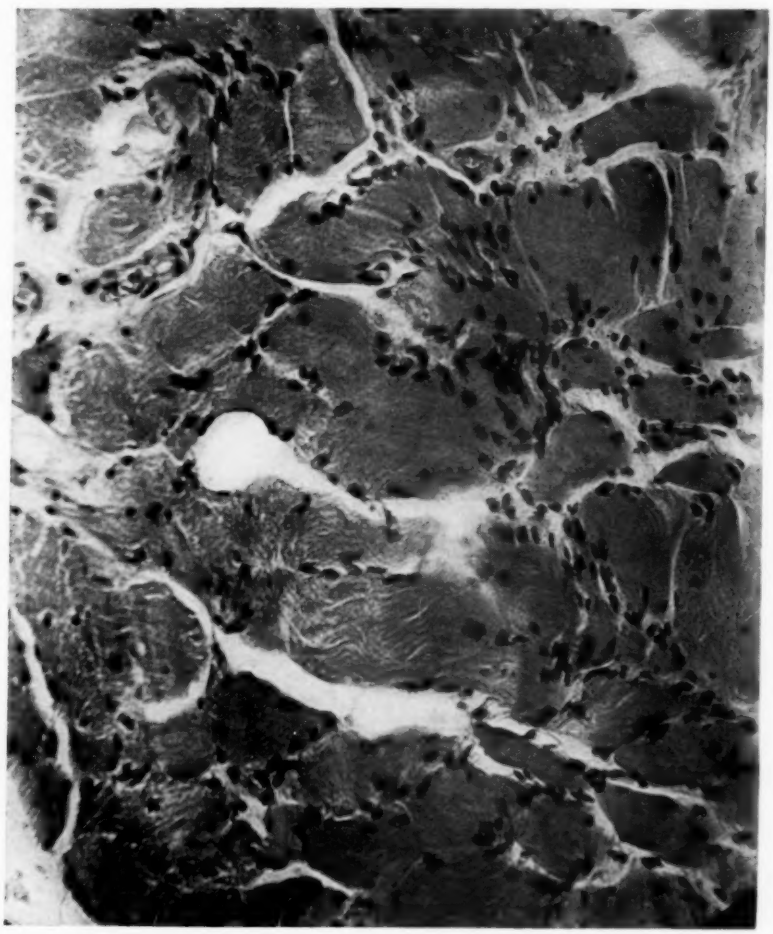


FIG. 7. (High power). Case 11. (J. M.). Male, age 54. Duration of arthritis three years. Fusiform joint swelling. Spleen not enlarged. Mild anemia. W.B.C. 21,850. A biopsy specimen shows irregular atrophy of the voluntary muscle. There is a marked increase in the interstitial nuclei and a slight old chronic myositis.

years' duration. He had originally developed pain and a fusiform swelling of the right knee, which had later spread to the left knee. Since that time, the ankles had become involved and subsequently almost all the joints of his body. The past history was otherwise uneventful.

Physical examination: Revealed an undernourished, adult male not acutely ill. The extremities revealed slight fusiform swelling of the fingers and wrists, and atrophy of the dorsum of the hands, with extensive fusiform swelling of both knees

and ankles. His examination was otherwise negative. The liver and spleen were not palpable, and there was no enlargement of the lymph glands noted.

Laboratory findings: The routine blood Kahn test was negative. His blood count showed a hemoglobin of 56 per cent, 5,640,000 red blood cells, 21,850 white blood cells. Differential smear showed 80 per cent polymorphonuclear cells, 10 per cent monocytes, 9 per cent basophiles and 1 per cent eosinophiles. The urine on admission showed a 1 per cent albumin, numerous white blood cells and 20 to 30 red blood cells per high power field. The diagnosis made was chronic pyelonephritis and hydroureter, in addition to a chronic active prostatitis. A biopsy of the calf muscle, obtained on March 3, 1936, showed us significant changes in the skin. There was irregular atrophy of the muscle with increased stroma cells and a still active chronic myositis. The inflammatory process was non-selective for the vessels (figure 7). His white blood cell count later returned to 10,550 before his discharge. Roentgen-rays of the knees showed the arthritis, involving both knees and both feet, primarily atrophic in type.

Case 12. A white male (R. A.), aged 36, was admitted to the University Hospital June 1, 1936, complaining of pain, swelling and stiffness of the joints. The attacks of swelling, heat, redness, and tenderness of the joints began at the age of 11 at which time he was confined to bed for one year. On admission the most painful joints were the elbows, shoulders, and right knee. All the joints involved were stiff with marked limitation of motion. He had lost 70 pounds during the one and one-half years prior to admission, during which time he had had occasional "fever." The history otherwise was negative.

Physical examination: Revealed an undernourished white adult male, chronically ill. All the joints except the spine showed fusiform swelling. There was a flexion deformity of the elbows and knees. The arms were held at the side and the hips were extended. Heart and lungs were negative. The liver and spleen were not palpable and there was no lymphadenopathy. The examination was otherwise non-essential.

Laboratory findings: Routine blood Kahn test was negative. Several urine examinations were negative. Complete blood count on admission showed 89 per cent hemoglobin, 5.4 million red blood cells, and 7,200 white blood cells. The differential count showed 60 per cent polymorphonuclears, 1 per cent basophiles, 1 per cent eosinophiles, 24 per cent lymphocytes and 14 per cent monocytes. A biopsy of a calf muscle on June 16, 1936 showed the dermis was without inflammatory reaction; there was a slight fatty and simple atrophy of voluntary muscle with a relative increase in interstitial nuclei; numerous phagocytes with hemosiderin in them were seen around the small blood vessels, suggesting a previous local hemorrhage.

Discussion

Splenomegaly in Arthritis. Although Felty first described the entire complex, its several features have been recorded separately by others. Chauffard [12] in 1896, and Herringham [13] in 1909, described splenomegaly and hepatomegaly in association with arthritis. Still [14] in 1897 described a syndrome, seen in children, of anemia, enlarged glands and enlarged spleen in association with chronic progressive enlargement of the joints, which has since been called "Still's disease." Giffin,[15] in writing of diseases of the spleen, stated that splenomegaly sometimes occurs in chronic arthritis and called it chronic infectious splenomegaly. Ward [16] described a leukopenia and a low grade eosinophilia occurring in chronic septic splenomegaly. McCrae,[17] in 1904, reported an enlargement of the spleen in four of 110 cases of arthritis deformans. Hench [18] found that splenomegaly occurred

in about 1 per cent of the cases of rheumatoid arthritis, and Dawson [19] reports that it occurs in between 10 and 15 per cent of the cases.

The pathological findings in the spleen in cases of "Felty's syndrome," where splenectomy has been performed or autopsy done, show great similarity. Hanrahan and Miller [2] described hyperplasia of the endothelial cells lining dilated sinuses, an increased number of plasma cells in the pulp spaces, and very large Malpighian bodies with germinal centers in proportion. Craven's [5] case showed dilated sinuses filled with red blood cells. The splenic pulp had many plasma cells and large mononuclear phagocytes. The Malpighian bodies were enlarged with prominent germinal centers. Price and Schoenfeld [6] and Reich [10] described a diffuse chronic splenitis. Singer and Levy [8] likewise described the findings of a chronic septic splenitis in their two cases.

Whereas eight of the 12 cases described above in our series had an enlarged spleen in association with their rheumatoid arthritis, there is a microscopic study of the spleen available on only one. This was Case 3 described under Group I. This patient came to autopsy and the pathologist submitted the following description of the spleen: "Hyalin material, apparently amyloid, in many of the follicles. Numerous bone marrow giant cells in the sinusoidal spaces."

None of the pathologic findings in the spleens of our cases and those described by others are indicative, we believe, of anything more than a chronic infection, most probably of a generalized nature.

Leukopenia in Arthritis. In six of the 110 cases of arthritis deformans reported by McCrae,[17] a leukocyte count of 5000 or less was recorded. Eaton [20] found a leukopenia in 22 per cent of 250 cases, the differential formulae showing a neutropenia (under 60 per cent) in 43 per cent and an eosinophilia in 10 per cent. Dawson [19] reports that a leukopenia often develops in long continued chronic cases of rheumatoid arthritis and Hench [11] likewise states that in the more chronic stages the leukocytes tend to be definitely low (4000 to 6000 per cu. mm.).

The duration of the rheumatoid arthritis in the four cases of this group of 12 which showed a leukopenia was eight, one, six, and nine years respectively. Although the average duration of disease in these 12 cases was 6.9 years, we agree with those who believe that the leukopenic response is indicative of a long standing chronic infection, and not an integral part of any specific syndrome.

Bone Marrow Response. The sternal bone marrow in the case reported by Price and Schoenfeld [6] showed some hyperplasia, a few bone marrow giant cells, and an active myelosis. The bone marrow in one of the two cases reported by Singer and Levy [8] showed marked congestion and signs of atrophy in the fatty portions. The reticulum was inconspicuous and the cellularity was 37 per cent. The marrow of the other case showed dilated sinuses and congestion. The reticulum cells were swollen and the cellularity was 80 per cent. A sternal puncture in Williams' case [9] showed numerous

normoblasts and nucleated red blood cells. There were some stem cells, a few granulocytes, rare mature polymorphonuclear leukocytes, and numerous megakaryocytes. The atypical findings in the bone marrow of Williams' case [9] suggested to him a primary blood dyscrasia, in which there is an arrest in the maturation of the polymorphonuclear leukocytes.

A specimen of bone marrow was obtained in one case of this series, Case 3 in Group I, which patient came to autopsy. After decalcification the rib, sternum and vertebral body showed bone marrow which was actively cellular, having numerous megakaryocytes and the various types of young blood cells. The cellularity varied from 60 to 80 per cent.

Whereas the number of cases with bone marrow findings reported elsewhere when added to our own is very small, the picture found in these few does not seem characteristic to us of anything other than the result of a chronic infection.

Lymph Glands. A biopsy of a lymph gland in one case reported by Felty [1] showed chronic lymphadenitis. The hemolymph nodes in Price and Schoenfeld's case [6] showed myeloid changes with moderate edema and deposits of hemosiderin. An inguinal node biopsied in one of the two cases reported by Singer and Levy [8] showed chronic lymphadenitis. In the other case, dilated sinuses and hyperplasia were found in the abdominal, inguinal and cervical glands.

Two of our cases have a microscopic study of a lymph gland recorded. One case (Case 4, Group I) showed a chronic hyperplastic lymphadenitis with marked hyperplasia of the sinus reticulum. The lymph gland of the other case (Case 2, Group III) showed chronic hyperplastic lymphadenitis with marked hyperplasia of the reticuloendothelium.

We do not consider the changes found in our own cases, or in the others reported, as significant of anything other than a chronic infection, not of any specific nature.

Calf Muscle Biopsies. In Group I of our series, three of the four cases showing rheumatoid arthritis, splenomegaly, leukopenia and adenitis (Cases 1, 2 and 3) showed on biopsy of the skin and calf muscle: (1) atrophy of the epithelium; (2) fibrosis of the corium; (3) increase in interstitial nuclei of the muscle fibers, and (4) small perivascular infiltrations throughout the corium and muscle. It may be reasoned that the atrophy, fibrosis, and increase in interstitial nuclei are the result of disuse in these cases of long standing arthritis, yet we believe that these three features may likewise be manifestations of a chronic generalized infection. We further believe that the perivascular infiltration found in the corium and muscle more conclusively points toward the presence of some generalized infectious process.

The patients in Group II (Cases 5, 6, 7 and 8) were selected because they presented, in addition to chronic rheumatoid arthritis and splenomegaly, a normal or elevated leukocyte count instead of a leukopenia. Calf muscle biopsies on all four of these cases showed two with an atrophy of the epithelium, fibrosis of the corium, increase in interstitial nuclei and again the

perivascular lymphocytic infiltration. In other words, the pathologic findings in these two groups are almost identical even though the cases of Group II lack the leukopenia.

Again, as another means of control for the patients in Group I, we selected four cases (Group III, Cases 9, 10, 11 and 12). These four cases all showed a chronic rheumatoid arthritis, but without any splenomegaly or leukopenia. The calf muscle biopsies of these four cases showed atrophy, fibrosis and increase in the interstitial nuclei and, in addition, Case 9 showed a slight perivascular infiltration, Case 10 showed definite small foci of perivascular infiltration, chiefly lymphocytic, and Case 11 showed an old chronic myositis which is still active.

In summarizing these pathologic findings, we believe that the changes noted in Cases 1, 2 and 3 of Group I, Cases 6 and 7 of Group II, and Cases 9, 10 and 11 of Group III are practically identical and therefore indicative of the same generalized chronic infectious process regardless of the variation in the clinical picture of these three groups.

We likewise believe that the incidence noted in the literature of leukopenia occurring in chronic rheumatoid arthritis, and of splenomegaly in chronic rheumatoid arthritis is of such an extent that the factor of this combination (arthritis, splenomegaly, leukopenia) occurring together in the same patient, is a result of chance rather than indicative of any specific syndrome. We therefore concur with the viewpoint of Dawson [19] and others that there is no justification for the segregation of these cases, and that the use of the term " Felty's syndrome " should be discontinued.

Conclusions

1. Calf muscle biopsies from patients showing chronic arthritis, leukopenia, and splenomegaly, presented a similar pathologic picture to that seen in biopsies from those cases showing only chronic rheumatoid arthritis.

2. The disease process in cases of chronic rheumatoid arthritis either with or without leukopenia and splenomegaly is a generalized one.

3. Inasmuch as leukopenia or splenomegaly is not infrequent in patients with chronic rheumatoid arthritis, the occurrence of " Felty's syndrome " in patients with arthritis is but a matter of chance.

4. We believe Felty gave the correct interpretation to the syndrome when he said " the several features are manifestations of one pathological process caused by a noxa which simultaneously affects the joints, the spleen and the blood leukocytes." This " noxa " seems to be the unknown etiological agent of rheumatoid arthritis and the whole syndrome is a not unexpected complex.

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SUBCLINICAL PULMONARY TUBERCULOSIS; A PRESENTATION OF FORTY CASES*

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THE individual destined to develop pulmonary tuberculosis will in most instances have it diagnosed no earlier today than years ago. Though the death rate continues to show a yearly drop, evidence indicates that this favorable occurrence has resulted from factors other than an early diagnosis.[1, 2, 3] Efforts in the past have been directed primarily toward studying disease in its later stages as it occurs at the bedside, when symptoms and physical signs have made their appearance, and later, unfortunately, in a still more advanced stage, at the postmortem table. Relatively little is known at present of subclinical disease, of methods for its discovery, or of the factors that determine its subsequent course. This field is wide and unexplored, and a scientific approach to it offers the medical profession the privilege of serving mankind more adequately by making possible the treatment of disease in its early rather than in its later stages.

Because illness and health continue to be associated with the presence or absence of symptoms and signs, our mental habits make it difficult to treat and consider seriously the potentialities of a pathological process not yet extensive enough to alter the individual's well being. The fallacy of associating disease only with its manifestations as they occur later in the course was well appreciated and probably best expressed over a century ago by a French physician, Gaspard Laurent Bayle, when he wrote of tuberculosis: "This manner of considering phthisis is just as ridiculous as that of a naturalist who seeing a young oak tree would refuse absolutely to give it this name because it did not yet show all its generic and specific characteristics. Moreover the oak which has just grown out of the ground, although it is a very feeble plant, is none the less a tree whose trunks will acquire a great deal of strength. It is the same with phthisis: in the beginning it seems scarcely a slight indisposition: in its last stage it strikes down the strongest man, it devours, consumes and reduces to a skeleton those whose plumpness, freshness, and health appeared unalterable."

Tuberculosis as it affects the individual will always continue to be a very serious personal problem. A falling death rate in the general population offers little solace to the victim of tuberculosis who did not have the advantage of early diagnosis. For him the problems of treatment are multiplied, require a longer period of cure, and give a prognosis that is definitely less favorable.

To insure early diagnosis all the infected, as determined by a properly

* Received for publication November 24, 1939.

I wish to express my appreciation to Miss Ethel Thewlis, Dr. Gertrude Stewart, and Miss Thekla Klatt for having done the total and differential leukocyte counts in this study.

administered Mantoux test, must be examined by the roentgen-ray at regular intervals, either by film or fluoroscopy. At the present time, unfortunately, known tuberculous infection is not seriously enough considered. Since, among infected students under observation in the period from 1933 to 1939, 1.6 per cent of the infected were found with already active tuberculosis on admission to the university or developed it subsequently, it is reasonable to assume that at least 10 per cent of the infected will develop active demonstrable disease during their life time. The fact is appreciated that all the infected do not react to the Mantoux test,[4] but to date, in over 20,000 students who have been tuberculin tested, no individual negative to tuberculin has reported to the student clinic and been found to have active tuberculosis. The recent work of Lumsden [5] concerning the adequacy of the tuberculin test in determining infection deserves to be considered; but until individuals with active minimal or subminimal tuberculosis are found who fail to react to tuberculin the test will continue to be of great practical value in making examination necessary only for those showing a positive reaction. With the advent of large group surveys the tuberculous lesion is being found in its earliest visible form, and, once found, the question regarding its status immediately arises.

The Early Infiltrate

The problem of the early pulmonary infiltrate is to determine whether it is pathologically active or healed. The determination of the status of the early lesion, now more frequently being found when no larger than 3 to 10 millimeters in diameter, or present in the form of so-called apical "caps" or pleuritis, cannot be done without considerable effort and without often repeated examination. Such lesions, though occurring in apparently healthy individuals and frequently considered of no consequence, are in fact pathologically active as determined by laboratory methods. Even though these laboratory studies prove to be negative at first, where such lesions have been found, they should continually be viewed with suspicion, and detailed examinations should be repeated at intervals of three to six months. In the past reliance usually has been placed on serial roentgen-ray films. But entire dependence upon roentgen-ray films is not without objection, for a process may be active, as indicated by the presence of tubercle bacilli in the gastric contents, and yet may show no significant roentgen-ray change for a period of years. The process is, however, potentially dangerous. Moreover, with serial films as the only measure of activity, further lung invasion and destruction are frequently allowed to occur and the prognosis is made less favorable.

The minute size of the early infiltrate gives no assurance of benignity. An active lesion, though small, repeatedly seeding tubercle bacilli in the surrounding tissues, offers the constant and dangerous threat of progressive tuberculosis. It becomes important, therefore, to take immediate advantage of all methods which give additional information regarding the exact status

of the lesion and the course it may subsequently pursue. Unfortunately, at the present time, because observation has been limited to relatively few cases, little is known regarding the early lesion and whether its course is usually benign or progressive. Furthermore, little is known of the factors that may alter its course.

Procedure

Individuals showing small infiltrates, either by roentgenogram or fluoroscopy, are hospitalized for a short period, at which time a history is taken, a complete physical examination is made, and the temperature and pulse, though seldom found elevated, are determined at four-hour intervals. Laboratory studies consist of aspiration of the fasting morning gastric contents,[6] determination of the blood sedimentation rate according to the method of Cutler,[7] and repeated study of the total and differential blood counts. The sputum is routinely studied, but in early cases tubercle bacilli are rarely found by this method of examination.[6]

The fasting gastric contents are aspirated on three successive mornings by means of a size 16 French nasal catheter, passed either through the nose or by mouth. By means of a Luer syringe from 10 to 15 c.c. of gastric contents are usually obtainable. If nothing can be aspirated, 15 c.c. of sterile normal saline are placed in the stomach by means of the tube, and after 15 minutes this fluid is again withdrawn, placed in a sterile container, and sent to a laboratory for examination by direct stain and guinea pig inoculation. This method is more satisfactory than the usually advocated gastric lavage. The large amount of fluid obtained by lavage is cumbersome to handle, especially if the specimen must be sent to the laboratory by mail, and is also less easily prepared for examination. It should be added that the tube, syringe and specimen bottle should always be sterilized by boiling for at least 20 minutes before being used. In our series of over 70 cases, showing lesions which were minimal or subminimal in extent, the sputum when obtainable was negative in all instances, whereas direct stains of the centrifuged gastric contents were positive in 18 per cent, and guinea pig inoculation with gastric centrifugate gave positive findings in 72 per cent of the cases. In moderately or far advanced active cases, when at least three aspirations are done, on no occasion has a negative result been obtained.

The adequacy of gastric aspiration combined with guinea pig inoculation has not been widely appreciated, nor has sufficient use been made of this valuable method of examination. Experience shows that:

1. If positive, it establishes the diagnosis and indicates whether any lesion is active.
2. It is the best indicator that the minimal and subminimal lesions are tuberculous and active.
3. It is an important aid in differential diagnosis.
4. It is the most accurate gauge in measuring the success of treatment and how long treatment should be continued.

5. It is an important factor in considering the need of surgical treatment.

6. It is a measurement of infectiousness and helps determine the patient's relationship to society.

7. It makes possible a more accurate prognosis.

Determination of the *blood sedimentation rate* is a relatively simple laboratory procedure. No corrections were made for anemia, for in no instance did this exist to an appreciable degree. The sedimentation rate, though showing an increase before the temperature is elevated or before symptoms are manifest, is usually found, as will subsequently be shown, to be normal in the early stages of tuberculosis.

Concurring in Medlar's [8] thesis: "The only logical way to determine whether the leukocytic reaction in the tuberculous is of real significance is to compare the interpretation of the leukocytic picture with the interpretation of the status of a case as judged by the clinical progress and by roentgenographic findings," the leukocytic picture was studied and correlations made with other laboratory methods.

The leukocytic reaction has been interpreted as determined by the Medlar leukocytic index.[9, 10] Graphic representations of the total number of neutrophiles, lymphocytes and monocytes have also been made. Medlar's method of interpreting the leukocyte reaction has been chosen in preference to the methods of Blackfan,[11] Cunningham [12] and Webb [13] in whose interpretations the monocytes and lymphocytes or their ratios alone are considered.

Many of the leukocyte counts showed no marked variation over a period of months, or at least not enough change to be considered as significant. In these instances (table 1) the average Medlar index of the total number of weekly counts adequately indicates the leukocyte response. To better portray the leukocyte reaction in certain cases, the entire series of weekly counts are presented separately.

The blood counts were done by an especially trained technician and the students studied reported at the same designated hour and day at weekly intervals. The patient, on reporting for the test, was requested to rest on a bed for at least one-half hour before blood for examination was taken.

Method

For the total count, blood from an ear puncture was diluted 1 to 20 with 1 per cent acetic acid in pipettes certified by the National Bureau of Standards. The pipette was shaken one-half to one minute immediately after the dilution of blood, and two to three minutes before filling the counting chamber (Spencer's Bright-Line Improved Neubauer Chamber; cover glasses, size 20 by 24 mm., thickness 5 mm.; all certified by the National Bureau of Standards). Two pipettes were used for each count, filling one chamber from each pipette, after discarding three drops and counting the four large-ruled corner squares in each chamber. If the number of cells counted in one chamber varied by more than 10 from that in the other chamber, the pipettes were reshaken and the chambers filled again. The average of the cells counted from both pipettes was multiplied by 50 to obtain the total number of white cells per cubic millimeter of blood.

TABLE I

Presentation of Data

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
1 Hoge 73876 22	10–14–38 to 5–27–39 Wt. Stat.	10–14–38 11–14–38 1–20–39 4–12–39 Average	1 4 3 3 2.8	9	34.8 10–14–38 to 4–12–39	Feb. 1939	+	Thoracoplasty with good collapse. Surgical treatment not successful in converting gastric contents.
2 Norv 75764 24 M.	9–19–38 to 1–13–39 Wt. Stat.	10–17–38 1–13–39 Average	1 2 1.5	12	18.1 10–14–38 to 1–13–39	Nov. 1938	+	Small soft infiltrate in both clavicular areas. Rapid retrogression of lesion following institution of San. treatment.
3 Luer 77106 22 M.A.	4– 2–36 to 1–19–39 Wt. Gain 29 lb.	4– 9–36 10–25–37 12– 4–37 1–17–39 Average	13 13 6 7 9.8	25	17.1 10–25–37 to 6– 6–38	Apr. 1936 Oct. 1937 Feb. 1938 June 1938 Jan. 1939	+ + + + +	Bilateral apical and clavicular lesion with marked retrogression under San. regimen. Fibrotic lesion persists which shows no recent significant change.
4 Land 77192 18 M.A.	2– 3–37 to 6– 2–39 Wt. Gain 16 lb.	2– 3–37 4–12–37 10–17–37 5–17–38 4–15–39 Average	10 7 1 10 8 5.2	51	34.2 2– 3–37 to 6– 2–39	Feb. 1937 Nov. 1937 May 1938 Nov. 1938 Feb. 1939	+ + 0 + +	Lesion first noted 1933 with periods of retrogression and extension. Left pneumothorax instituted 1937 apparently with excellent results. Because of persistent free bacilli, pneumothorax is being instituted on right this summer. (1939)
5 Gree 79975 20 M.A.	9–18–33 to 3–29–37 Wt. Gain 11 lb.	2– 7–36 6–20–36 2–10–37 3–29–37 Average	17 19 15.5 21 18.1	10	28.7 2– 6–36 to 3–31–37	Feb. 1937 June 1937 Feb. 1938	+ + +	Progressive lesion resulting from first infection. Returned to Univ. on two occasions because of satisfactory clinical picture. Unfavorable subsequent course on each occasion.
6 Ann 79831 18 M. to M.A.	9–16–33 to 6– 8–37 Wt. Gain 23 lb.	10–13–34 12–21–34 2–20–35 2– 3–36 6–15–36 10–14–36 3– 3–37 6– 5–37 Average	11 8 8 11 9 10 13 11 10.1	23	Separate Presentation 3– 3–37 to 6– 8–37	Mar. 1936 Dec. 1936 May 1937	+ + +	Massive pleural effusion in Dec. 1933 with subsequent development of progressive tuberculosis from subminimal apical lesion. Process has never caused symptoms subsequent to effusion, and recent films April 1939 show continued change.
7 Aud. 82226 20 M.	9–26–34 to 1–18–35 Wt. Gain 24 lb.	10–20–34 4– 5–35 3–24–36 6– 2–36 11– 5–36 5–24–37 11–16–38 3–16–38 11–16–38 Average	3.5 2 4.5 5 6 8 9 5 4 5.3	33	20.4	Mar. 1938 Nov. 1938	+ 0	Disseminated lesions in both apices and clavicular regions showing alternate periods of extension and retrogression.
8 Gloz 82916 18 M.	9–21–34 to 3– 2–38 Wt. Gain 14 lb.	9–10–34 3–12–35 11–27–35 2–22–36 5–27–39 12– 8–36 3–23–37 10– 6–37 2–23–38 Average	15 7 9 10 9 8.5 11 12 5.5 9.6	21	24.5 12– 9–36 to 6– 1–38	Oct. 1934 May 1935 Oct. 1936	+ + 0	Minimal infiltrate at right apex with subsequent healing by fibrosis and calcification.

TABLE I—*Continued*

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
9 Clem 83312 25 M.	9–22–34 to 1–13–39 Wt. Gain 16 lb.	5–16–36 1–14–37 10– 3–37 4–12–38 9–23–38 6–24–38 1–13–39 Average	11 2 4 3 3 3 3 5.2	31	23.8 10– 4–37 to 1–13–39	May 1936 Dec. 1937 May 1938 Sept. 1938 Jan. 1939	+ 0 0 + +	Subminimal lesion first noted in 1934. Extension in 1936. Subsequent Sanatorium treatment with retrogression. Slow extension since Sept. 1938. Return to Sanatorium July 1939.
10 Swen 84566 34 M.	10–17–34 to 5– 6–39 Wt. Gain 25 lb.	10–17–34 1–23–35 12–28–35 9–30–36 4–20–37 11– 2–37 3–11–38 5– 1–39 Average	2 5 4 3 5 9 3.5 3.5 4.2	12	12.3 11– 9–38 to 5– 1–39	Dec. 1936 Apr. 1937 Mar. 1938 May 1939	+ 0 0 0	Sanatorium treatment prior to 1934. Residual infiltrate right clavicular region with extension in Dec. 1936. San. treatment with retrogression of lesion. Recent films, June 1939, show only calcification.
11 Soff. 87246 21 M.	9–21–35 to 5–31–38 Wt. Gain 20 lb.	4– 6–37 5–10–37 6– 7–38 10–13–37 5–29–38 Average	7 10 7 5 3 6.4	37	62.9 Septic picture completely at variance with gast. cont. and x-ray. 2– 7–37 to 5–23–38	Apr. 1937 June 1937 Apr. 1938	0 0 0	Minimal right clavicular infiltrate first noted Sept. 1935. Some extension Feb. to May 1937. Retrogression, May 1937 to June 1938. Recent film, July 1939, shows further retrogression.
12 Lair 87375 20 M.	12– 8–37 to 6– 5–39 Wt. Gain 13 lb.	1–16–38 3–19–38 5–11–38 6–11–38 10–27–38 4–24–39 6– 2–39 Average	4 3 2 4 0.5 5 2 2.9	37	27.8 12– 8–37 to 6– 5–39	June 1938 Nov. 1938 Jan. 1939 Apr. 1939	+ + 0 +	Recent infection, fall of 1936, from tuberculous roommate. Development of lesion with subsequent extension five months after infection. Recent films, May 1939, show no extension since Oct. 1938.
13 Stef. 88261 21 M.	9–25–35 to 6– 1–39 Wt. Gain 4 lb.	10–25–35 12– 4–36 4– 7–37 6– 6–37 8–31–37 11–29–37 1– 3–38 4–14–38 1–30–39 5–11–39 Average	4.5 4 4 7 13* 4.5 3 3 9 7 5.9	116	22.7 12–15–36 to 6– 1–39	Dec. 1936 Feb. 1937 Apr. 1937 May 1937 Jan. 1938 May 1938 Feb. 1939	+ + + 0 + + +	Interlobar fibrotic band noted on right in Sept. 1935. Subsequently small lesions noted in left clavicular region and above band on rt. Rest treatment with retrogression. Subsequent minimal extension in the right apex. Process active for five years without production of symptoms. Entered Sanatorium June 1939.
14 Holm 88578 20 M.	9–27–35 to 6– 8–39 Wt. Gain 20 lb.	3–21–36 2–26–37 5–27–37 10–22–37 2–10–38 10–24–38 5–18–39 Average	2 2.5 3 5 3 1 2 2.7	28	9.8 3–21–36 to 6– 8–39	Mar. 1936 Mar. 1938 Mar. 1939	0 0 0	Soft minimal left subclavicular infiltrate first noted Sept. 1935. Subsequent retrogression with fibrosis and development of 6 mm. calcification.
15 McClel 89973 19 M.A.	9–23–35 to 5– 5–39 Wt. Loss 6 lb.	10– 8–35 1–27–36 9–15–36 1–17–37 5–17–37 10– 4–37 2–21–38 10– 3–38 5– 4–39 Average	11 10 11 6 11 15 10 2 25 11.2	48	46.4 1–30–37 to 5– 4–39	May 1937 Oct. 1937 Mar. 1938 May 1938 Oct. 1938 May 1939	+ + 0 + + +	Lesion intermittently but inadequately treated since 1935. No apparent change in films from 1935 to Feb. 1939. Extension with small cavitation Feb. to May 1939.

TABLE I—*Continued*

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
16 Koltun 91862 19 M.	9–18–36 to 5–25–39 Wt. Gain 7 lb.	11–22–37 10–14–38 1–28–39 4–28–39 Average	15 3 4 6 7	24	21.3 10–19–38 to 5–25–39	Nov. 1937 Jan. 1939	0 0	Contact tuberculous uncle 1932. Pleural effusion 1933. Film Sept. 1936 negative. Fluoroscopy Nov. 1937 showed small infiltrate. San. treatment 9 months. Films Oct. 1938 and June 1939 show continued retrogression.
17 Tite 93081 18 Hilum tbc.	9–24–36 to 5–16–38 Wt. Gain 22 lb.	3–11–37 3–22–37 4– 1–37 11–29–37 1–15–38 3–22–38 5–16–38 Average	23 9 8.5 5 4 5 4 8.3	16	17.9 1–17–38 to 5–16–38	Mar. 1937 Dec. 1937 Mar. 1938	+ + +	Negative film Sept. 1936. Massive pleural effusion March 1937. Subsequent involvement of right hilum glands but with no visible parenchymal change. No recent films but patient writes—July 1939—that he is well and working.
18 Suku 93257 23 M.	10– 2–36 to 6– 7–39 Wt. Gain 10 lb.	10–22–36 2– 1–37 6–11–37 10–11–37 3–22–37 6– 9–39 Average	4 8 9 7 11 2.5 6.4	46	44.6 2– 1–37 to 4– 4–38	Nov. 1936 Feb. 1937 Mar. 1938 Apr. 1939	+ + 0 0	Contact with tuberculous roommate summer 1936. Soft lesion 22 × 24 mm. noted in left clavicular region Oct. 1936. Serial films since have shown complete resolution of the infiltrate.—June 1939.
19 Kub 93502 20 M.	9–25–36 to 4–27–37 Wt. Stat.	11– 4–36 12– 9–36 4–27–37 Average	9 7 3.5 6.5	10	39.4 11– 4–36 to 4–27–37	Nov. 1936	0	Soft infiltrate first noted in left apex Oct. 1936. Subsequent extension apparent in Feb. 1937. No further change to June 1937. Failed to return to school. Recent film, 1939, shows retrogression of lesion.
20 Marv. 93631 22 M.	9–26–36 to 7– 7–39 Wt. Gain 7 lb.	10–26–36 12–16–36 1–25–37 6– 8–37 11– 5–37 4–23–38 5–18–39 Average	3 8 2 6 3 3 4 3.2	50	32.6 10–26–36 to 5–19–29	Oct. 1936 Nov. 1937 Apr. 1938 May 1939	+ + + 0	Soft infiltrate first noted rt. apex Oct. 1936. Subsequent extension Jan. to June 1937. Retrogression noted Nov. 1937. Extension again in April 1938. Retrogression since that time with little residual evidence of infiltrate.—July 1939.
21 Fried 94383 17 M.A.	9–19–36 to 6– 2–38 Wt. Stat.	10–14–36 12– 2–36 5– 1–37 11– 2–37 3–19–38 Average	6 7 6.5 9 3 6.3	51	26.8 1–27–37 to 6– 2–38	Oct. 1936 Nov. 1937 Mar. 1938	+ + +	Former San. patient, considered cured. During interval Sept. 1936 to May 1938 both retrogression and extension of small infiltrates in the clavicular areas were noted. Letter June 1939 indicates patient still clinically well.
22 Boncyk 93719 18 M.	9–26–36 to 6–10–39 Wt. Gain 12 lb.	10–16–36 1–20–37 1–27–37 5–25–38 10–18–38 1–10–39 3–22–39	5 11 6.5 3 1 3 7	33	16.2 Ave. index before pneumothorax 21.1 After pneumothorax 14.6. 1–27–38 to 5–29–39	Jan. 1937 Dec. 1937 Feb. 1938 June 1938 Oct. 1939 Jan. 1939 Mar. 1939	0 + + 0 0 + 0	Former San. patient. Small lesion left apex Sept. 1936 with extension noted Nov. 1937. Free bacilli in stomach. Pneumothorax instituted June 1938. Marked retrogression of lesion June 1939.
23 Hard 94875 20 M.	9–22–36 to 6– 4–38 Wt. Stat.	10–13–36 11–23–36 3–11–37 6–11–37 10– 7–37 6– 3–38 Average	7 5 9 8 5 4 6.3	29	29.2 10–14–36 to 5– 9–38	Oct. 1936 Feb. 1937 Feb. 1938	0 0 0	Two small infiltrates 12 × 18 and 10 × 12 mm. noted in right subclavicular region Sept. 1936. Subsequent gradual resorption with only fibrotic strands remaining June 1938.

TABLE I—*Continued*

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
24 Mart 94935 19 M.	9–22–36 to 12–13–38 Wt. Gain 7 lb.	10–19–36 3–16–37 4–30–37 6–10–37 10– 4–37 3–16–38 10– 5–38 Average	8.5 11 6.5 7 10 8 3.5 7.8	33	21.6 10–19–36 to 10–13–39	Oct. 1936 Mar. 1938 Oct. 1938	0 0 0	Scattered small infiltrates in right apex and clavicular region first noted Oct. 1936. Extension in Oct. 1937 with subsequent marked retrogression and fibrosis of lesion Oct. 1938.
25 Merk 95004 22 M.	9–22–36 to 5–31–39 Wt. Stat.	6–10–38 9– 1–38 12– 2–38 3–24–39 6– 6–39 Average	4 4 6.5 7 8.5 6.	23	17.7 10–13–38 to 5–31–39	June 1938 Sept. 1938 Dec. 1938 June 1939	0 + 0 0	Recent infection with development of visible progressive tuberculosis limited to apical pleura and a 5 × 5 mm. density in the right clavicular region.
26 Gust 95466 29 M.	2–18–37 to 3–23–39 Wt. Gain 4 lb.	3– 1–37 5–11–37 10– 4–37 2–18–38 5–11–38 3–23–39 6– 3–39 Average	12 9 6 8 9 7 9 7.6	29	33.9 10– 7–37 to 6– 1–38	Mar. 1937 May 1937 Oct. 1937 Feb. 1938 Nov. 1938 Mar. 1939	+ + + + + +	Films taken at 4 month intervals from Feb. 1937 to March 1939 show minimal apical lesions undergoing both slight progression and retrogression.
27 Kilb 97740 17 M.	9–16–47 to 5–29–39 Wt. Gain 13 lb.	10–15–37 12–18–37 3–10–38 6– 7–38 10–14–38 5–31–39 Average	5 5 2 2.5 1 2.5 3	45	18.8 10–14–37 to 5–16–39	Oct. 1937 Apr. 1938 Nov. 1938 Mar. 1939	0 + + 0	Oval 15 × 22 mm. density right subclavicular area noted in Sept. 1937. Retrogression at original site with extension at the periphery May 1939.
28 Gleb 98167 23 M.	9–18–37 to 6– 5–38 Wt. Gain 20 lb.	2– 8–39 5– 5–39 5–24–39 Average	0.5 2 2 1.5	16	32 2– 8–39 to 6– 5–39	Feb. 1939 May 1939	+ +	Film Sept. 1937 showed thickened pleura at the left base, and calcified deposits in both lungs. No change to May 1938. In Feb. 1939 soft infiltrate in right clavicular area noted. Film May 1939 showed marked retrogression. Free bacilli persist.
29 Elson 98179 23 M.	9–18–37 to 5– 5–39 Wt. Gain 9 lb.	10– 7–37 3–11–38 6– 3–38 4–29–39 Average	10 4 6 5 6.3	18	35.6 10– 7–37 to 6– 3–38	Nov. 1937 May 1938	0 0	Small infiltration left clavicular region first noted Sept. 1937. Retrogression of lesion from Sept. 1937 to June 1938. Further retrogression noted June 1939.
30 Thad 98202 18 M. to M.A.	9–18–37 to 2– 6–39 Wt. Stat.	10–11–37 12–10–37 9–30–38 2– 6–39 Average	5.3 8 4 4 5.4	27	25 10–11–37 to 2– 6–39	Oct. 1937 Oct. 1938	+ 0	San. treatment 1935 to 1937. Apical infiltrates noted on enrollment Sept. 1937. Readmitted to San. Feb. to Aug. 1938. Re-enrolled Sept. 1938 with no apparent change in lesion. In Jan. 1939 developed tbc. in left wrist and cavity at apex of lung. Returned to Sanatorium.
31 Beck 98356 22 M.	9–20–37 to 6– 7–39 Wt. Gain 12 lb.	12–13–38 4–15–39 6– 1–39 Average	4.5 5 7 5.2	23	16.3 12–13–38 to 6– 7–39	Dec. 1938 Apr. 1939	+ 0	Film Sept. 1937 negative. Dec. 1938 soft lesion found in left subclavicular region. Subsequent films Jan. 1939 to June 1939 showed marked resorption of lesion.

TABLE I—*Continued*

Case Age	Period of Observation Weight	Blood Sedimentation Rate		Leukocyte Reaction		Gastric Aspiration with Pig Inoculation		Roentgen-Ray Study
		Date	Rate	No.	Ave. Medlar Index	Date	Result	
32 Loch 100459 22 M.	11–17–37 to 6–16–39 Wt. Gain 14 lb.	1–13–38 3– 3–38 6– 2–38 10–12–38 5– 5–39 Average	8.5 6 2 0.5 3 4	25	25.4 Average index before pneumothorax 23.3 After pneumothorax 27.9. 1–12–38 to 5–31–39	Jan. 1938 Oct. 1938 May 1939	+ 0 0	Film of Nov. 1937 showed soft 18 × 22 mm. lesion in right clavicular region. Cavity noted Mar. 1938 which became larger in June 1938. Pneumothorax instituted in July 1938. Cavity closed Oct. 1938. Films of June 1939 show residual 6 by 9 mm. lesion.
33 Cast 101659 21 M.	9–16–38 to 6– 3–39 Wt. Stat.	10– 6–38 12– 6–38 3– 1–39 5–16–39 Average	5 6 13* 11† 11.2	17	30.8 10– 6–38 to 5– 9–39	Oct. 1938 Mar. 1939	0 0	Small infiltrates both apices and in right subclavicular region. Calcium in rt. lung and hilum glands. From Sept. 1938 to June 1939 definite retrogression in subclavicular lesion. No change in calcium or at apices.
34 Rye 102038 21 M.	9–19–38 to 6–10–39 Wt. Gain 8 lb.	10– 7–38 1–12–39 4– 4–39 5–19–39 Average	4 5.5 5 10.5 6.3	19	35.6 10– 7–38 to 5–23–39	Oct. 1938 Apr. 1939	0 +	Soft infiltrate in right apex noted Sept. 1938. No change in serial films including those of June 1939.
35 Hony 102507 26 M.A.	9–22–38 to 5–24–39 Wt. Stat.	10–11–38 2–25–39 4–27–39 5–24–39 Average	8 15 9 12 9.8	24	14.9 10–11–38 to 5–24–39	Oct. 1938 Mar. 1939	+ +	Sanatorium patient 1930–1937. Discharged apparently cured. Enrolled Sept. 1938. Several old lesions upper half of left lung which showed intermittent change to June 1939. Note good leukocyte response.
36 Hig 102871 17 M.	9–15–38 to 6– 9–39 Wt. Gain 6 lb.	11– 1–38 5–23–39 Average	1 4 2.5	20	44.3 11– 1–38 to 5–18–39	Nov. 1938 May 1939	0 Refused test	Small infiltrate with 3 mm. cavity noted Sept. 1938 in right clavicular area. Serial films to June 1939 show retrogression with closure of cavity.
37 Gil 103748 21 M.	9–19–38 to 2– 1–39 Wt. Gain 10 lb.	10–20–38 1–11–39 2– 1–39 Average	3 6 5.5 4.8	9	21.6 10–20–38 to 2– 1–39	Oct. 1938	+	Small soft lesion noted in left apex Sept. 1938. Slight extension occurred prior and subsequent to San. treatment Feb. 1939. Pneumothorax instituted April 1939.
38 Smy 104278 18 M.	8–20–38 to 6– 8–39 Wt. Gain 8 lb.	12– 9–38 5– 4–39 Average	9 5 7	16	25.3 12– 8–38 to 6– 8–39	Nov. 1938 Feb. 1939 June 1939	+ 0 0	Small infiltrate right clavicular region noted Sept. 1938. No change in appearance to June 1939.
39 Swt 104571 18 M.	9–21–38 to 6–12–39 Wt. Gain 3 lb.	10–21–38 1–11–39 6–12–39 Average	1 3 5 3	17	24.2 2– 3–39 to 6–12–39	Oct. 1938 Jan. 1939 Apr. 1939	+ + 0	Soft infiltrate right clavicular region noted Sept. 1938 with subsequent marked retrogression of lesion to July 1939.
40 DrE 27 M.	2–10–37 to 5–29–39 Wt. Stat.	2–12–37 3– 1–37 1– 9–38 6–28–39 Average	2 3 5 5 3.8	29	14.3 1–20–37 to 5–29–39	Feb. 1937 Mar. 1938 Nov. 1938	not done 0 0	Films of Jan. 1936 negative. Bilateral small apical infiltrates Feb. 1937 with subsequent complete resolution of lesion June 1939.

* Ear infection.
† Acute respiratory infection.

Cover glass smears were made for the differential count by touching a clean 22 mm. cover glass (soaked in concentrated nitric acid, washed successively in water, soap solution, water, and stored in 95 per cent alcohol until they were wiped dry at the time of the count), to a small drop of blood from the ear puncture, being careful not to touch the ear. Another cover glass was placed diagonally on this, and the two pulled apart just before the blood stopped spreading. An even smear is obtained in this way, the thickness of which can easily be varied. The smears were stained with Wright's stain (National Aniline Dye and Chemical Co., New York), and three smears, mounted on a slide with immersion oil, were covered as completely as possible.

The percentages of monocytes, neutrophiles, small lymphocytes, large lymphocytes, young lymphocytes, eosinophiles, and basophiles reported were based on the 400 leukocytes counted for each sample. All mononuclear cells with granular, muddy blue cytoplasm were considered monocytes, regardless of the shape of the nucleus. No effort was made to differentiate between filamented and non-filamented neutrophiles, but large lymphocytes were distinguished from small lymphocytes by their size, being about the size of neutrophiles in the same or nearby fields. Young lymphocytes were distinguished by their very blue cytoplasm, and, usually accompanying this, their larger size and lighter-staining nuclei. Occasionally a cell of relatively large size was found which had very blue cytoplasm and light-staining nucleus sometimes containing still lighter areas (nucleoli); these were reported as "large young cells," since they were too young to determine their origin.

Interpretation of Data

The fact is appreciated that it is hazardous to interpret laboratory data concerned with a pathological process which has not yet completed its usual long chronic course. For absolute accuracy, interpretation should be deferred until the process is completely healed (a practical impossibility) or until the patient has died from the disease. Since the ideal is impossible it is nevertheless important and valuable to study the course of the pathologic process during a "period of the disease."

A favorable clinical course, as indicated by a gain in bodily weight (table 2), absence of fever, and a general feeling of well being, though desirable, should not be the basis for judging the patient's progress. Weight loss, however, should be considered with concern. In the one individual of this series who lost weight the tuberculous process was progressive. Judgment based on a favorable clinical course, rather than on critical laboratory study and consideration of the underlying pathology, offers an adequate explanation of the frequent so-called "breakdowns" and "recurrences." These unfortunate occurrences represent in most instances extensions of active tuberculous foci which have never healed. Insurance companies, penalized by poor risks, appreciate more than physicians the frequency and seriousness of recurrences among the apparently cured. Their judgment is based on eventualities, and "clinical benignity" and "apparently cured," though suggestive at close range of satisfactory progress, have not proved to be sufficient or positive evidence of real cure. To protect themselves, underwriters have found that the elapse of sufficient time is their best practical guide in determining that tuberculosis is "sufficiently cured" to warrant the risk of contract.

TABLE II

Correlation of Laboratory Methods

Case No.	Weight Pounds	Erythrocyte Sedimentation Rate	Leukocyte Reaction	Guinea Pig Gastric Content	Roentgen-Ray*
1	0	Normal	Unfavorable	+	N.C.
2	0	N.	Favorable	+	R.
3	+29	N.	Fav.	+	R.
4	+16	N.	Unf.	+	R.
5	+11	Inc.	Equivocal	+	E.
6	+23	Inc.	Unf.	+	E.
7	+24	N.	Fav.	+ to −	E.
8	+14	N.	Eq.	+ to −	R.
9	+16	N.	Eq.	+	E.
10	+25	N.	Fav.	+	R.
11	+20	N.	Unf.	0	R.
12	+13	N.	Eq.	+	E.
13	+ 4	N.	Eq.	+	E.
14	+20	N.	Fav.	0	R.
15	− 6	Inc.	Unf.	+	E.
16	+27	N.	Eq.	0	R.
17	+22	N.	Fav.	+	E.
18	+10	N.	Unf.	+ to −	R.
19	0	N.	Unf.	0	E.
20	+ 7	N.	Unf.	+ to −	R.
21	0	N.	Eq.	+	E.
22	+12	N.	Fav.	+ to −	R.
23	0	N.	Eq.	0	R.
24	+ 7	N.	Eq.	0	R.
25	0	N.	Fav.	+ to −	E.
26	+ 4	N.	Unf.	+	E.
27	+13	N.	Fav.	+ to −	R.
28	+20	N.	Unf.	+	R.
29	+ 9	N.	Unf.	0	R.
30	0	N.	Eq.	+ to −	E.
31	+12	N.	Fav.	+ to −	R.
32	+14	N.	Eq.	+ so −	R.
33	0	Iuc.	Unf.	0	R.
34	+ 8	N.	Unf.	+	N.C.
35	0	N.	Fav.	+	E.
36	+ 6	N.	Unf.	0	R.
37	+10	N.	Eq.	+	E.
38	+ 8	N.	Eq.	+ to −	N.C.
39	+ 3	N.	Eq.	+ to −	R.
40	0	N.	Fav.	0	R.
Totals	Gain 407 Loss 6	N 36 90% I 4 10%	F 12 30% U 14 35% E 14 35%	P 18 45% P to N 12 30% N 10 25%	R 22 55% E 15 37.5% N 3 7.5%

* R.—Retrogression; E.—Extension; N.C.—No change.

Since the erythrocyte sedimentation rate was normal in 36 of 40 or 90 per cent of the active cases, the test, when normal, is of limited value as an aid in determining the status of the subclinical lesion. It offers little of the assurance, so generally accepted in the past, that the lesion is either benign or inactive. As indicated in table 3, the course of the lesion in the small group (10 per cent) having an increase in rate was less favorable than in those with a normal response.

TABLE III

Erythrocyte Sedimentation Rate
Forty Cases

Normal	% of Cases	Roentgen-Ray		
36	90%	Retrogression	21	58.3%
		Extension	12	33.3%
		No change	3	8.3%
Increase		Roentgen-Ray		
4	10%	Extension	3	75.0%
		Retrogression	1	25.0%

In interpreting the leukocyte response, as shown in tables 2 and 4, the cases have been arbitrarily divided into three groups: those showing a favorable leukocytic index with an average index below 20; those with an unfavorable index, above 30; and the equivocal group in which the index falls between 21 and 30.

Those with indices between 21 and 30 are considered equivocal because normal healthy individuals with negative Mantoux tests and normal chest roentgenograms may fall in this group. Two such students volunteering to report for a weekly blood count for a period of three and six months were found to have an average leukocytic index of 22 and 29 respectively. Medlar,[14] in studying the leukocytic reaction in normal individuals, found that in 113 or 24 per cent of the 478 counts done, the average index registered between 21 and 30.

TABLE IV

Leukocyte Reaction
Forty Cases

Favorable	% of Cases	Roentgen-Ray		
12	30%	Retrogression	9	75%
		Extension	3	25%
Unfavorable		Roentgen-Ray		
14	35%	Retrogression	8	57.2%
		Extension	5	35.7%
		No change	1	7.1%
Equivocal		Roentgen-Ray		
14	35%	Extension	7	50.0%
		Retrogression	6	42.9%
		No change	1	7.1%
Unfav. + Equiv.		Roentgen-Ray		
28	70%	Retrogression	15	53.6%
		Extension	11	39.3%
		No change	1	7.1%

In table 4 the leukocyte reactions are compared with the progress of the lesion as determined by the roentgenogram. In the favorable leukocytic index group, 9 of 12, or 75 per cent of the cases, showed retrogression of the lesion. In two of the three cases withdrawing from school because of initial

extension, but with favorable leukocyte reactions, the subsequent pathological course of the lesion was favorable. Both slight extension and retrogression occurred in the third case in this group in which the leukocyte count was favorable. This patient (Case 35) had received sanatorium care for seven years and was considered cured. She is clinically well, but her gastric contents are positive. The favorable leukocyte reaction, barring a pathological accident, probably offers some assurance that, though the lesion is active, there is little danger of rapid extension. From these data it appears that a favorable leukocyte reaction may be reliably accepted as indicating that the pathological process is healing, or, as in the exceptional case, the process is being controlled. In no instance where the total number of lymphocytes or the lymphocyte percentage was high has the pathological process taken a significantly unfavorable course.

An unfavorable leukocyte reaction (table 4), however, does not necessarily mean an unfavorable prognosis, for in 14 cases classified as having unfavorable leukocyte reactions, retrogression occurred in 8, or 57.2 per cent. Two of these eight had high and ominous leukocytic indices. Case 18, with an average leukocytic index of 44.6 showed complete resolution of the infiltrate. Case 11, with an average leukocytic index of 62.9 also showed retrogression of the lesion, and though no recent roentgenogram of the lungs is available, information from the patient's father indicates that if extension has occurred, it has not been sufficient to interfere with his marriage or health. Objection to presentation of this case may be made on the basis that proof that the lesion is tuberculous is not at hand since the gastric contents were always negative. The roentgen-ray appearance and site of the lesion, however, favor the diagnosis of tuberculosis (figure 1).

In the group of 14 cases with equivocal leukocytic reactions, the results approximated those of the unfavorable group. Combining the equivocal and unfavorable groups, table 4, no significant changes in the figures occur. Since retrogression of the lesion occurred in 53 per cent of the combined unfavorable and equivocal groups, an unfavorable or questionable unfavorable leukocyte reaction does not portend, in the majority of subclinical cases, the predicted unfavorable course.

The weekly blood counts of five cases are presented (table 5). Numbers 1 and 2, representing Cases 2 and 14, indicate a satisfactory lymphocyte response which, when present, indicates, with few exceptions, a favorable prognosis. Number 3, representing Case 18, is presented to show that the absence of a good lymphocyte response does not necessarily indicate an unfavorable course, for in this instance complete resolution of the infiltrate occurred.

Number 4, representing Case 6, shows a very bizarre leukocyte reaction for a period of three weeks, during which time and subsequent thereto an extension of the lesion occurred. The patient was without symptoms, and though the count suggested an acute mononucleosis, the fatigue and adenopathy accompanying that condition were absent. On one occasion the per

cent and total number of monocytes were higher than the per cent and total number of either the lymphocytes or neutrophiles. The details in each case are given in table 1.

Number 5, representing Case 12, is of especial interest since it represents the leukocyte reaction following known infection, with the subsequent development of an active lesion. The lesion reached its maximum extent in October 1938, since which time there has been some retrogression. The leukocyte reaction might be interpreted as unfavorable though during recent months there has occurred no further extension of the process.

FIG. 1. Apical infiltration in Case 11.

This particular case raises the question of the benignity of first infection tuberculosis. If we accept the formerly negative Mantoux test as evidence of the absence of previous infection, this case represents a progressive pathological process resulting from the first infection. The subsequent course of this particular lesion cannot be foretold, but if its course follows that of five other similar cases, progression of the lesion may be anticipated. That the first infection is usually benign is substantiated by the large number of infected individuals who fail to develop progressive tuberculosis, but the statement that tuberculosis resulting from first infection is always benign [15] and that treatment has no influence on the primary complex should be accepted as an opinion rather than as a fact. Quoting Myers [16] in his recent article: "It is now known that treatment has no influence on this primary complex, as the walls form around the bacilli in the same way when the per-

TABLE V

Weekly Blood Counts in Five Patients

Case 2. Favorable leukocyte reaction with subsequent marked retrogression of lesion.

Leukocyte Reaction No. 1

Date	Total	M	%	L	%	N	%	Index
10–14–38	12,000	810	6.8	3780	31.5	6570	54.8	19
10–21–38	11,150	1422	12.8	3512	31.5	5268	47.3	16
10–28–38	10,950	685	6.3	3680	33.5	5900	53.8	14
11– 4–38	9,650	773	8.0	2510	26.0	6050	62.8	24
11–11–38	10,200	485	4.8	3140	30.8	5950	58.3	18
11–18–38	9,550	980	10.3	2720	28.5	5300	55.5	19
11–25–38	11,650	905	7.8	3180	27.3	7300	60.3	25
12– 2–38	10,300	900	8.8	2630	25.5	6450	62.3	24
12– 9–38	10,500	710	6.8	2970	29.3	6460	61.5	22
12–16–38	7,350	625	8.5	2460	33.5	3725	51.0	11
1– 6–39	11,500	720	6.3	4025	35.0	6300	54.8	11
1–13–39	10,350	905	8.8	3390	32.8	5775	55.8	14

Case 14. Favorable leukocyte response with healing by fibrosis and calcification.

Leukocyte Reaction No. 2

Date	Total	M	%	L	%	N	%	Index
2–26–37	8,875	666	7.5	3239	36.5	4770	53.8	10
3–31–37	9,750	878	9.0	4217	43.3	4509	46.3	1
4– 7–37	8,225	576	7.0	3208	39.0	4277	52.0	7
4–14–37	8,075	404	5.0	2342	29.0	5208	64.5	22
4–28–37	10,175	763	7.5	4833	47.5	4579	45.0	0
5–27–37	8,200	820	10.0	2624	35.8	4346	53.0	9
6– 3–37	7,725	521	6.8	2839	36.8	4172	53.0	9
10–22–37	7,275	455	6.3	2474	34.0	4165	57.3	13
11–11–37	8,100	324	4.0	2633	32.5	5063	62.5	19
12– 2–37	7,050	159	2.3	2362	33.5	4442	63.0	17
12– 6–37	7,750	388	5.0	3790	36.0	4427	57.3	11
1–14–38	7,450	298	4.0	2924	39.3	4060	54.5	8
2–10–38	7,550	504	6.5	2790	36.0	4340	56.0	11
3–24–38	10,400	754	7.3	4004	38.5	5382	51.8	8
6–17–38	8,500	489	5.8	2465	29.0	5355	63.0	22
10–24–38	9,200	875	9.5	3295	35.8	4925	53.5	10
10–31–38	8,150	510	6.3	2820	34.5	4590	56.3	12
11–23–38	8,200	555	6.8	3260	39.8	4260	52.0	6
12– 5–38	7,800	370	4.8	3320	42.5	4055	52.0	4
12–12–38	8,050	362	4.5	2920	36.3	4670	58.0	12
1– 9–39	7,850	432	5.5	3560	45.3	3750	47.8	1
5– 2–39	8,750	438	5.0	3760	43.0	4375	50.0	3
5–18–39	7,000	385	5.5	2625	37.5	3880	55.5	9
5–26–39	7,850	392	5.0	3140	40.0	4300	54.8	8
6– 8–39	8,000	640	8.0	3140	39.3	4050	50.5	6

Table 5 continued on page 2300.

son goes about the usual activities of life as when he is placed on strict bed rest or collapse therapy. Nothing destroys the tubercle bacilli or reduces the allergy of the tissues. Apparently nothing has any influence on the later escape of bacilli from the primary foci. The infant or child with primary tuberculosis on treatment, including strict bed rest, may have meningitis,

TABLE V—*Continued*

Case 18. Continued unfavorable leukocyte response with complete resolution of infiltrate.

Leukocyte Reaction No. 3

Date	Total	M	%	L	%	N	%	Index
2–22–37	8,625	647	7.5	1423	16.5	6339	73.5	44
2–24–37	5,850	351	6.0	1053	18.0	4285	73.3	41
2–26–37	7,400	574	7.8	1628	22.0	5051	68.3	31
3– 1–37	8,225	802	9.8	1193	14.5	5922	72.0	49
3– 3–37	9,000	585	6.5	1328	14.8	6908	76.8	51
3– 8–37	8,700	653	7.5	1523	17.5	6375	73.5	42
3–10–37	10,275	1361	13.3	1541	15.0	7115	69.3	45
3–17–37	10,400	598	5.8	1846	17.8	7748	74.5	42
3–22–37	9,875	617	6.3	1778	18.0	7158	73.5	42
3–24–37	10,875	924	8.5	2420	22.3	7395	68.0	31
3–29–37	11,900	1160	9.8	1785	15.0	8747	73.5	52
3–31–37	10,325	800	7.8	1368	13.3	8028	77.8	60
4– 2–37	10,875	1006	9.3	2066	19.0	7640	70.3	37
4– 5–37	8,075	626	7.8	1211	15.0	5976	74.0	49
4– 7–37	8,575	493	5.6	1544	18.0	6367	74.3	41
4–14–37	10,650	639	6.0	1331	12.5	8334	78.3	62
4–19–37	9,850	345	3.5	1084	11.0	8225	83.5	76
4–21–37	10,150	1066	10.5	1573	15.5	7232	71.3	45
4–26–37	11,100	805	7.3	1776	16.0	8297	74.8	43
5– 3–37	8,500	510	6.0	1404	16.8	6375	75.0	44
5– 5–37	12,050	452	3.8	1808	15.0	9555	79.3	56
5–10–37	9,125	662	7.3	1620	17.8	6684	73.3	41
5–12–37	8,525	171	2.0	1684	19.8	6479	76.0	38
5–17–37	8,200	472	5.8	1538	18.8	6068	74.0	39
5–19–37	10,300	798	7.8	1004	9.8	8389	81.5	100
5–26–37	10,450	810	7.8	1541	14.8	7890	75.5	50
6– 2–37	10,550	633	6.0	1583	15.0	8071	76.5	50
6– 7–37	10,875	625	5.8	1822	16.8	8211	75.5	44
10–11–37	8,875	600	6.8	1376	15.5	6678	75.3	48
10–18–37	7,875	295	3.8	1831	23.3	5453	69.3	30
10–25–37	8,375	628	7.5	1591	19.0	6009	71.8	38
11– 1–37	8,975	292	3.3	2064	23.0	6440	71.8	31
11– 8–37	9,575	527	5.5	2801	29.3	6080	63.5	22
11–15–37	10,350	492	4.8	2044	19.8	7633	73.8	37
11–22–37	8,700	370	4.3	1805	20.8	6416	73.8	35
11–29–37	9,450	732	7.8	1654	17.5	6851	72.5	41
12– 6–37	11,200	476	4.3	2208	20.1	8176	73.0	39
12–13–37	10,050	276	2.8	2286	22.8	7186	71.5	31
1–10–38	7,750	407	5.3	1647	21.3	5464	70.5	33
1–17–38	8,850	575	6.5	1859	21.0	6217	70.3	33
3– 7–38	8,000	460	5.8	1740	21.8	5600	70.0	32
3–14–38	11,250	618	5.5	1630	14.5	8800	78.3	56
3–21–38	8,450	696	8.3	2050	24.3	5510	65.3	27
4– 4–38	8,800	485	5.5	1650	18.8	6470	73.5	39

Table 5 continued on page 2301

miliary tuberculosis or tuberculous pneumonia as readily as the one leading an active life. Moreover, the person who has had drastic treatment for the primary complex apparently is just as likely to fall ill later from acute or chronic forms of the disease as the person who has had no treatment for the primary disease."

Critical analysis of the statements made in the above paragraph necessitates careful consideration as to whether sufficient evidence is at hand to

TABLE V—*Continued*

Case 6. Extension of infiltrate during time of bizarre leukocytic reaction with high monocyte and lymphocyte counts, and low neutrophile count.

Leukocyte Reaction No. 4

Date	Total	M	%	L	%	N	%
3– 3–37	9,800	785	8.3	1789	18.3	6958	71.0
3–10–37	8,975	494	5.5	1817	20.3	6484	72.3
3–17–37	4,025	523	13.0	1228	30.5	2073	51.5
3–24–37	6,650	2261	34.0	1895	28.5	2394	36.0
3–31–37	7,150	2860	40.0	2234	31.3	1913	26.8
4– 7–37	5,600	1582	28.3	2198	39.3	1638	29.3
4–12–37	7,150	483	6.8	2467	34.5	3950	55.3
4–28–37	8,575	579	6.0	2165	25.3	5724	66.8
5– 6–37	7,225	415	5.8	1969	27.3	4606	63.8
5–13–37	8,175	715	8.8	2248	27.5	5089	62.3
5–20–37	8,250	660	8.0	1588	19.3	5940	72.0
5–27–37	9,450	756	8.0	2032	21.5	6591	69.8
6– 3–37	9,000	810	9.0	2160	24.0	5670	63.0
6– 8–37	9,325	909	9.8	2448	26.3	5665	60.8

Table 5 continued on page 2302.

justify such conclusions. The fact that a large majority of first infection lesions heal does not justify the conclusion that a similar course occurs in all such lesions. Doubt exists as to whether we can actually determine that a process is no longer pathologically active. Accepted evidence (no change in serial roentgenograms) that a lesion is healed has been proved to be erroneous. This error is suggested in Myers' discussion when he mentions "escape of bacilli from primary foci," and again when he says: "The infant or child with primary tuberculosis on treatment, including strict bed rest (no exogenous reinfection possible) may have meningitis, miliary tuberculosis or tuberculosis pneumonia as readily as the one leading an active life." A lesion with these potentialities can hardly be considered benign. Many will question whether adequate evidence is available to justify the conclusion that treatment of the primary complex is without influence on the process. Tubercle formation with destruction of normal tissue occurs in both first infection and reinfection tuberculosis and though usually not progressive in either case, it appears both inconsistent and invalid that the same pathological process should be seriously considered and treated in the second instance and not in the first. Furthermore, without proof of when infection occurred, distinction between lesions resulting from first infection or reinfection is frequently not possible and should not be attempted.

At present, by observation of the early subclinical lesion, evidence is accumulating that, in a small percentage of cases, the pathologic process resulting from the first infection never completely heals, though for years there may be no indication of its activity other than the occasional presence of tubercle bacilli in the gastric contents as determined by guinea pig inoculation. Potentially, such a lesion is always a menace, although it is often erroneously

TABLE V—*Continued*

Case 12. Patient infected fall of 1937 by tuberculous room-mate. Mantoux formerly negative became positive and visible tuberculous lesion was first noted in March 1938. The above counts represent his leukocyte response since infection. Films showed extension until January 1939, since which time some resolution has occurred. Gastric contents positive, patient never ill, no fever, weight gain 13 lb. Count may be considered either equivocal or unfavorable.

Leukocyte Reaction No. 5

Date	Total	M	%	L	%	N	%	Index
12– 8–37	7,600	703	9.3	2109	27.8	4427	58.3	21
12–15–37	8,450	613	7.3	1838	21.8	5746	68.0	31
3–10–38	7,600	589	7.8	1720	22.5	5110	67.3	30
3–30–38	10,100	960	9.5	2145	21.3	6895	68.3	32
4– 6–38	8,600	881	10.3	2625	30.5	4900	58.0	18
4–13–38	7,850	765	9.8	2415	30.8	4530	57.8	17
5– 4–38	8,150	590	7.3	1510	18.5	5960	73.3	40
5–11–38	9,450	755	8.0	1654	17.5	6875	72.8	42
5–18–38	8,450	655	7.8	1920	22.8	5700	67.5	29
5–25–38	10,250	769	7.5	1820	17.8	7100	69.3	39
6– 1–38	8,800	462	5.3	1670	19.0	6360	72.3	38
6– 9–38	11,350	965	8.5	1985	17.5	8370	73.8	42
10–13–38	6,400	416	6.5	2016	31.5	3648	57.0	16
10–27–38	7,000	630	9.0	2020	28.8	4100	58.5	20
11– 3–38	8,500	553	6.5	1660	19.5	6100	71.8	37
11–10–38	9,050	595	6.5	2680	29.3	5600	61.3	21
11–17–38	6,950	730	10.5	2040	29.3	4050	58.3	20
12– 1–38	8,950	715	8.0	2510	28.0	5450	61.0	22
12– 8–38	7,700	520	6.8	2470	32.0	4550	59.0	17
12–15–38	7,850	610	7.8	2220	28.3	4810	61.3	22
1– 5–39	11,700	555	4.8	2280	19.5	8700	74.3	41
1–12–39	7,450	745	8.0	2440	29.5	4870	58.8	20
1–19–39	12,550	817	6.5	3740	29.8	7726	61.5	27
1–26–39	9,700	680	7.0	2690	27.8	6000	62.0	22
2–14–39	10,200	690	6.8	2270	22.3	6950	68.0	31
2–21–39	7,400	720	9.8	1205	16.3	5250	71.0	47
2–27–39	6,800	730	10.8	2340	34.3	3480	51.3	10
3– 6–39	7,600	513	6.8	2030	26.8	4925	64.8	24
3–13–39	10,050	603	6.0	2965	29.5	6230	62.0	21
3–20–39	8,600	840	10.8	1680	19.5	5525	64.3	34
2–27–39	7,500	620	8.3	2010	26.8	4700	62.5	23
4– 3–39	9,150	410	4.5	2060	22.5	6425	20.3	31
4–10–39	8,300	685	8.3	1785	21.5	5550	66.8	31
4–25–39	8,150	775	9.5	2340	28.8	4910	60.3	20
5– 8–39	6,500	390	6.0	1450	22.3	4540	69.8	32
5–15–39	10,050	553	5.5	2180	21.8	7180	71.5	32
6– 5–39	6,450	613	9.5	1740	27.0	4050	62.8	23

considered benign, because of apparent but not real interruption in the continuity of the pathologic process. Proof that the continuity is not interrupted is indicated, as already stated, by the presence of bacilli in the gastric contents. Though the lesion resulting from first infection is usually benign, the development of visible evidence of tuberculosis soon after infection, as determined by a positive Mantoux test in one formerly negative, must be seriously considered. To the present time five such individuals have come under observation. All had known recent contact with open cases of tuberculosis, were previously negative to the Mantoux test, developed visible evi-

dence of tuberculosis on roentgenograms, and all had tubercle bacilli in their gastric contents. The only evidence of benignity in these five cases is that none is dead. Two are still receiving pneumothorax and sanatorium treatment; one is on the equivalent of sanatorium treatment at home; one, though showing no recent roentgen-ray change, continues to have positive gastric aspirations; and the other has recently developed, in addition to a clavicular lesion, subminimal infiltrates at the extreme apices. The lesson from these cases supports the opinion that the lesion resulting from the first infection can and in a certain percentage of cases does institute a pathologic process which may continue for years, eventually causing the individual's death.

TABLE VI

Gastric Contents
40 Cases

Guinea Pigs		Roentgen-ray		
Positive	% of Cases	Extension	11	61.2%
18	45%	Retrogression	5	27.7%
		No change	2	11.1%
Positive to Negative		Retrogression	7	58.4%
12	30%	Extension	4	33.3%
		No change	1	8.3%
Always Negative		Retrogression	9	90.0%
10	25%	Extension	1	10.0%

GASTRIC CONTENTS

As indicated in table 6, 30 of the 40, or 75 per cent, of the subclinical cases were positive by guinea pig inoculation. Where the roentgenogram fails to show changes from month to month, the presence of tubercle bacilli in the gastric contents is the only positive method of indicating that the lesion is both tuberculous and also active. Furthermore, we cannot assume, as we have in the past, that because no change is noted on serial roentgenograms the process is necessarily healed. One student with such a lesion has been under observation for a period of 28 months and, on the seven occasions in which the gastric contents have been aspirated, the results have always been positive.

Where the gastric contents originally have been found positive and have remained positive (table 6), extension occurred in 61 per cent of the cases, and only 28 per cent showed retrogression. Where conversion from positive to negative occurred, retrogression was noted in 58 per cent, and extension in 33 per cent of the cases. In the group always negative on gastric aspiration, retrogression of the lesion was noted in 90 per cent of the cases. The one individual in this group who showed extension (who withdrew from school in 1937) subsequently showed almost complete resolution of the infiltrate.

From the above it appears that examination of the gastric contents by guinea pig inoculation is the most accurate and valuable laboratory method

in determining the status and subsequent course of the subclinical tuberculous lesion.

Summary

The early tuberculous lesion occurs without producing a clinical picture. Its detection is dependent on repeated roentgen-ray examination of the apparently healthy. The early lesion having been found, the question regarding its status presents itself. Is the process tuberculous, and is it pathologically active or has it healed? Dependence on serial roentgenograms frequently requires the passage of considerable time, and fails to prove that the process is tuberculous. Furthermore, extension means further lung destruction and a less favorable prognosis. Methods, therefore, are desirable which will determine the status of the early lesion before further progression occurs.

Of available laboratory methods, the erythrocyte sediment rate was found to be normal in 90 per cent of the cases, and apparently gives little assurance that a lesion is either benign or inactive. The leukocyte reaction, where favorable, indicates a favorable prognosis. An unfavorable or equivocal leukocyte reaction, however, indicated an unfavorable course in only 50 per cent of the cases. Gastric aspiration with guinea pig inoculation is the most reliable method of proving both the diagnosis and activity of the lesion. The repeated presence of tubercle bacilli in the bronchial secretions usually indicates an unfavorable course. Conversion from positive to negative indicates a more favorable prognosis, and repeated absence of tubercle bacilli in the gastric contents is almost complete assurance of a favorable course.

Close observation and study by laboratory procedures indicate that the lesion resulting from first infection is not always benign and may cause progressive tuberculosis. Maximum information regarding subclinical tuberculosis is dependent on adequate and repeated use of laboratory methods. Relatively little is known of the early lesion or the factors that determine its subsequent course. Many of our present opinions probably will be found fallacious.

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HEMOLYTIC REACTIONS FOLLOWING TRANSFUSIONS OF BLOOD OF THE HOMOLOGOUS GROUP, WITH THREE* CASES IN WHICH THE SAME AGGLUTINOGEN WAS RESPONSIBLE†

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THE discovery [16, 17] in 1900 of the isoagglutination reaction was one of the most important steps in the history of blood transfusion, since when donors of the same blood group as the patient are used, transfusions are practically free from danger. Even after this discovery was generally adopted and applied, however, occasional hemolytic reactions continued to occur. In the earlier days, practically all of these reactions could be traced to mistakes in blood grouping (Bordley [4]) of the patient, donor or both, and even at the present time such unnecessary errors are made too frequently.‡ Besides the hemolytic reactions caused by the transfusion of blood of the improper group, others have resulted from the indiscriminate use of "universal" donors.[21, 5, 8, 11] In addition, hemolytic reactions have recently been encountered following transfusions in which patient and donor belonged to the same blood group. Evidently such cases are rare, since only about a dozen definitely established instances of this sort have been reported in the literature to date. (For a review of the literature see reference 37.) The hemolytic transfusion reactions belonging to this last category, namely, those due to "intragroup" incompatibility, are the subject of the present paper.

Case 1. The patient was a 52 year old woman, admitted to the surgical service of the Mercy Hospital on August 13, 1939, with the complaint of vomiting, fever and bilateral abdominal pain of eight hours' duration. At the operation, performed on the day of admission, a ruptured solitary ulcer of the ileum § and peritonitis were found. Resection of the ileum with anastomosis and appendectomy was performed.

The patient belonged to group O. The day after the operation (the second day in the hospital) the patient was given a transfusion of 500 c.c. of fresh citrated blood of group O. Later the same day a second transfusion of 300 c.c. of group O blood was given. A third transfusion of 250 c.c. of blood was given on the third day; a fourth transfusion of 500 c.c. on the eighth day; the fifth and last transfusion of 500 c.c. of blood on the thirteenth day. All of the transfusions were from different group O blood donors. Preliminary to each transfusion the bloods of the patient and prospective donor were cross-matched.

* Including case cited in addendum.

† Received for publication March 11, 1940.

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

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‡ With regard to suitable technic of grouping and cross-matching, cf. [38]

§ Separate report in press (Robinson, D. R.: Surg., Gynec. and Obst.).

There were no febrile reactions whatever to the first four transfusions. However, during the week following the operation the patient had a continuous temperature of 103° F., which might possibly have masked the symptoms of a mild reaction. Of significance is the observation that while the hemoglobin concentration rose from 60 per cent on the day of the operation to 82 per cent after the third transfusion, it soon dropped back to 65 per cent and continued to fall after the fourth transfusion. Fifteen minutes after the completion of the fifth and last transfusion there was a severe chill lasting about half an hour, accompanied by a rise in temperature to 104° F. By the next day the patient had hemoglobinuria and marked oliguria, and became noticeably jaundiced (van den Bergh—direct, immediate positive 2.0 units; icteric index 19). The blood urea concentration rose from normal before the transfusion to 163 mg. per cent. The hemoglobin continued to fall, reaching as low as 46 per cent, and despite alkalinization the patient died four days after the onset of the transfusion reaction. At the postmortem examination, microscopic sections of the kidneys showed lesions considered characteristic of hemolytic transfusion reactions, namely, the typical degenerative changes of the tubular epithelium and the presence in the lumens of the collecting tubules of casts of brownish, pigmented hematin material.

Before the last transfusion, two cross-matching tests (hanging drop method at 37° C.) were reported by the technician and intern as showing no clumping even for periods up to several hours. Unfortunately, the specimens taken before the transfusion had been discarded inadvertently, and these observations could not be rechecked. Blood obtained from the patient after the transfusion and also after death and a fresh sample of blood drawn from the donor for the last transfusion were tested by one of us (W.). It was possible to confirm the fact that both patient and donor belonged to group O. In the cross-match test, however, while no agglutination was observed in the mixture of donor's serum with patient's cells, by a special technic * (vide infra) it could be shown that clumping occurred when the patient's serum was added to the donor's cells. Evidently, therefore, the patient's serum contained a special agglutinin, unrelated to the common isoagglutinins, α and β. That we were not dealing with an autoagglutinin was established by the absence of agglutination in mixtures of the patient's serum with her own cells. With the technics commonly used the abnormal reactions would probably not have been detected.

The properties of the special agglutinin and the corresponding agglutinable property in human blood were then investigated. First of all it was noticed that the reactions were considerably weaker than the common isoagglutination reactions. Moreover, the reactions were most pronounced at low temperatures, no noticeable reaction at all occurring at 37° C. Hemolysis could not be elicited in vitro at any temperature, even after the addition of fresh guinea-pig complement. These properties of the antibody in the patient's serum are somewhat surprising, considering the fact that it was capable of causing a fatal hemolytic reaction (see below). The reactions were best elicited by mixing a drop of a 2 per cent suspension of sensitive cells with two drops of serum in a small test tube (inside diameter 7 mm.) and allowing the mixtures to stand for two hours in the refrigerator. An

* With the common slide technic the reactions were indefinite.

alternative suitable technic was to chill the mixture for a few minutes, then centrifuge. After gentle shaking, the sediments immediately broke up into a homogeneous suspension in the case of negative bloods, while rather large clumps easily visible to the naked eye persisted with positively reacting bloods. The reactions could easily be reversed by warming the tubes to 37° C.; on chilling, the reactions reappeared.

Blood samples from a number of different individuals have been tested with the patient's serum. Only bloods of group O were selected, on account of the presence in the serum of the isoagglutinins α and β, which precluded direct tests on bloods of the other groups. It was found that the great majority of bloods were agglutinated by the antibody in question. The agglutinable property involved proved to be unrelated to any of the agglutinogens M, N or P, as well as the agglutinogens A and B. Remarkably, however, the reactions coincided with those given by certain anti-rhesus immune rabbit sera, recently described by Landsteiner and Wiener [20] which define an agglutinable property of human blood designated as Rh.

As will be seen from table 1, in which are given some representative reactions, 14 bloods have been tested with both the patient's serum and the reagent prepared from anti-rhesus immune serum. The chance that the reactions of the two reagents should agree in every instance merely by accident is 1 in 2^{14} or about one in sixteen thousand. It is reasonable to conclude, therefore, that the agglutinable property demonstrated with the patient's serum is identical with Rh.

It is now possible to offer an explanation for the hemolytic reaction. The patient belonged to group O (Rh—). Since Rh+ bloods are about 6 or 7 times as common as Rh— bloods, most if not all the donors were probably of group O (Rh+). Apparently, to begin with, the patient had a weak anti-Rh hemolysin in his serum, undetectable by any of the common in vitro tests. This assumption would account for the short period of survival of the transfused blood cells, as indicated by the temporary nature of the rise in hemoglobin after the first few transfusions. While one may assume that the blood received in these transfusions was hemolysed too slowly to produce noticeable symptoms, the repeated injections of Rh+ blood served to stimulate the production of anti-Rh antibodies of higher titer, particularly after the fourth transfusion. Accordingly, the fifth transfusion of Rh+ blood gave rise to an acute hemolytic reaction.

Two questions are raised in connection with the above interpretation. The first is why such reactions are not encountered more frequently, as many patients, of whom about one-seventh would be Rh negative, are given repeated transfusions. The probable answer is that not all Rh— individuals are capable of producing Rh antibodies. Some special constitutional factor may be required—possibly the presence of preformed antibodies. In addition, the interval between transfusions must be long enough to permit an adequate rise in titer of the antibody. The second question is how it is possible for an antibody which in vitro produces agglutination only at low

TABLE I

Comparison of Reactions Obtained with Serum of Patient (Case 1) and with an Anti-Rhesus Immune Rabbit Serum

Bloods all group O Tests made with	Type M				Type N				Type MN				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Serum of patient	+++±	+++±	−	+++±	++	−	+++±	+++±	+++	−	++	+++±	+++	−
Anti-rhesus immune serum, diluted 10× and absorbed with half volume of packed sediment of blood No. 14	pos.	pos.	neg.	pos.	pos.	neg.	pos.	pos.	pos.	neg.	pos.	pos.	pos.	neg.

The strength of the agglutinations is indicated by the number of plus signs, +++ representing the maximum possible reaction, namely, the formation of a single large clump.

temperatures and of low titer to give rise to a fatal hemolytic reaction. Possibly the agglutinin found in the patient's serum is only an indicator of some supplementary, more subtle mechanism which is brought into play in the body before hemolysis can occur.

Shortly after the above study was completed, a second case, almost an exact counterpart of the first one, was seen at the Mercy Hospital.

Case 2. In January 1937, the patient was operated on for a perforated gastric ulcer at another hospital. The postoperative course was complicated by pneumonia and neutropenia, the total white count dropping as low as 3000. A transfusion was given and the white count rose. The patient was discharged after 43 days in the hospital. About six months later, the patient began to have attacks of headache, pain in the lower back and in the legs, these symptoms being accompanied by fever and leukopenia. During the six months before the present admission, the attacks became more frequent and more severe, and the patient had chills occurring at all hours of the day. The temperature ranged from subnormal up to 104° F. and the patient became subject to upper respiratory infections. On November 9, 1939, the patient's tonsils and adenoids were removed; he was discharged on November 11.

On November 22, 1939, the patient was readmitted to the Mercy Hospital on the service of Dr. Pincoffs, because of recurrence of chills and fever three days previously. On November 25, the patient, who belongs to group A, was given a transfusion of 200 c.c. of fresh citrated group A blood. About one hour after this transfusion he had a chill which was slightly more severe than those he had had on the previous few days. However, there was no history of hemoglobinuria. The temperature dropped to a subnormal level 12 hours later and remained subnormal for a week. The patient was given two other transfusions of 250 c.c. each on November 27 and November 30, respectively, both from the same group A donor, but not the donor who gave the blood on November 22. There were no untoward symptoms following these transfusions. The patient had no more chills and felt well until his discharge on December 7.

Two days later the patient was readmitted with the same complaints as formerly, namely chills, fever, headache, etc. On December 12, he was given a transfusion of 200 c.c. of citrated blood from the donor who had given the first transfusion on November 22 (21 days previously). Twenty minutes after this transfusion was completed, the patient presented the symptoms of a severe hemolytic reaction. Hemoglobinemia and hemoglobinuria were present. Almost immediately there was complete suppression of urine, and rather persistent vomiting, at times bloody, ensued. The bleeding and coagulation times were prolonged. The blood urea rose as high as 250 mg. per cent and the creatinine to 14 mg. per cent. After complete anuria for one week there was an output of only 50 c.c. on the eighth day and anuria again on the ninth day. Up to this point the patient had been treated with intravenous glucose, sorbital and diathermy. On the tenth day, following splanchnic block (separate report by Pincoffs and Peters [80]) there was an immediate outpouring of urine and the blood urea dropped to 45 mg. per cent; the creatinine to 1.9 mg. per cent. Thereafter the patient improved progressively.

Previous to each transfusion the bloods of the patient and the prospective donor were cross-matched by the hanging drop and centrifuge methods. After the hemolytic reaction occurred, blood samples taken from the patient and donor before and after the last transfusion were examined by one of us; also the blood of the donor who gave the second and third transfusion was tested. It was found that both donors belonged to group A, subgroup A_1 type M. On the other hand, the patient's blood belonged to group A, sub-

group A_2, type N. The idea that the difference in the subgroups or in the M–N types was responsible for the reaction could be eliminated at once. Careful analysis of the reactions of the patient's blood revealed that before the fourth transfusion it actually consisted of a mixture of two sorts of blood; namely, about 90 per cent A_2N blood and about 10 per cent A_1M blood.* This indicated that some of the blood from the previous three transfusions was still present in the patient's circulation, which would hardly be possible if either of the agglutinogens A_1 or M had anything to do with the transfusion reaction. Moreover, the proportion of foreign A_1M cells did not increase after the transfusion given on December 12, which showed that the blood injected on that day must have been completely destroyed.

TABLE II

Cross-Matching Tests of the Serum of the Patient (Case 2) with the Bloods of His Two Donors

Serum Separated From Patient's Blood Drawn	Patient's Own Blood	Tested Against Blood of Donor for 1st and 4th Trans. (Donor No. 1)	Blood of Donor for 2d and 3rd Trans. (Donor No. 2)
Before transfusion	Q.N.S.	±	Q.N.S.
2 days after transfusion	–	–	–
3 days after transfusion	–	–	–
4 days after transfusion	–	++±	–
5 days after transfusion	–	++±	–
6 days after transfusion	–	++±	–
7 days after transfusion	–	++±	–

The tests were made by mixing 2 drops of patient's serum with 1 drop of a 2 per cent blood suspension in a small tube, and allowing the mixtures to stand for two hours at a refrigerator temperature, after which time the reactions were read.

Q.N.S. = quantity not sufficient.

The most logical explanation for these findings was that although both donors were A_1M, for some reason the blood of the donor used for the first and last transfusions (donor 1) was incompatible, whereas the blood of the other donor (donor 2) was compatible. That this explanation is correct was established by the cross-matching tests. As is shown in table 2, the patient's serum before the fourth transfusion gave at best only a doubtful reaction with the blood of donor 1, and serum obtained shortly after the transfusion gave no reaction at all. However, on the fourth day following the transfusion and thereafter, it could be shown by the sensitive technic described that the patient's serum agglutinated the blood of donor 2 but not the blood of donor 1. No agglutination was observed in mixtures of the patient's cells with the serum of either donor.

A series of individuals was available whose bloods had been tested with the serum of the patient in case 1. Blood samples were drawn from these persons in order to ascertain whether or not the agglutinable property of the blood cells detected by the serum of the patient in case 2 corresponded with the agglutinogen Rh. As is shown in table 3, the reactions of the two sera are identical so that both sera contain the same antibody, anti-Rh.

* For the technic see: WIENER, A. S.: Blood groups and blood transfusion, pages 55–57.

TABLE III

Comparison of Agglutination Reactions Obtained with the Sera of the Patients of Case 1 and Case 2

Tests Made With	Bloods (All Group O) of Type													
	M			N		MN								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Serum From Patient in Case 1	−	+++	−	++	++	+++	++±	−	+++	+++	−	+++	++±	−
Serum From Patient in Case 2	−	++	−	++	++±	++	++	−	++	++	−	++	++±	−

Let us now summarize the second case in the light of the serological findings. A patient, group A (Rh—) was given a series of blood transfusions from two donors, one group A (Rh+) the other group A (Rh—). The first transfusion from the donor A (Rh+) gave rise only to a subclinical reaction. The following two transfusions from donor A (Rh—) were perfectly compatible, so that the donor's cells could be demonstrated in the circulation of the patient (with the aid of the M–N tests) for a long time afterwards. On the other hand, the blood from the first transfusion was gradually hemolysed and eliminated, this being accompanied by the appearance of Rh antibodies in the patient's plasma. Later, when a second transfusion of blood from the first donor, A (Rh+), was given, a hemolytic reaction followed. The long interval between the two transfusions from this donor probably allowed time for a fall in the titer of the anti-Rh agglutinins, so that these were not demonstrable either by the hanging drop or centrifuge technic before the last transfusion. The reason why the Rh agglutinins were not demonstrable immediately after the transfusion is that they had been completely absorbed by the Rh+ blood introduced into the recipient's circulation. By the fourth day, however, the antibodies had reformed in sufficient amount to be detectable.

That the property Rh is a true antigen is established by its capacity to stimulate the formation of immune antibodies in our two patients. The anti-Rh agglutinins in the patient's serum had the same properties as most other specific agglutinins, since its activity was not appreciably affected by heating at 56° C. for 30 minutes, and, as shown in table 4, it is absorbable

TABLE IV

Specific Absorption of the Agglutinin Anti-Rh

Tests Made With	Tested Against			
	Rh Positive Blood		Rh Negative Blood	
	1	2	3	4
Untreated Serum	++±	++±	−	−
Serum Absorbed with Rh+ Blood	−	−	−	−
Serum Absorbed with Rh− Blood	++±	++±	−	−

The absorptions were set up by mixing the patient's serum with one-third volume of packed washed cells in test tubes. After the mixtures had stood for an hour, the tubes were centrifuged in cups containing ice-water, and the supernatant serum pipetted off for the tests. Two drops of serum were mixed with one drop of cell suspensions (2 per cent) in small test-tubes and the readings made after these had stood for two hours in the refrigerator.

by Rh+ blood but not by Rh— blood. The serum from the patient in case 2 like that of the first patient reacted most strongly at low temperatures and not at body temperature. As is shown in table 5, even at ice-box temperature, the reactions were only of relatively low titer. Corresponding

TABLE V

Titration of the Anti-Rh Agglutinins in the Serum of Patient 2

Tested Against	Dilution of Patient's Serum				
	Undil.	1 : 2	1 : 4	1 : 8	1 : 16
Rh Positive Blood	++±	++	+±	±	−
Rh Negative Blood	−	−	−	−	−

Two drops of each serum dilution were mixed with one drop of cell suspension (2 per cent) and readings were made after the mixtures had stood for 2 to 3 hours in the refrigerator.

with the low titer of the anti-Rh antibody was its lability, for after only one month of storage in the refrigerator, the activity of the serum had diminished noticeably. On the other hand, serum obtained from the patient more than one month after the transfusion was almost as active as the sample originally tested. Three months later, however, the antibody could no longer be detected in the patient's serum.

Of interest is the relative incidence in the general population of Rh positive and Rh negative bloods. In addition to the bloods previously tested with the serum of patient 1, a series of group O and group A bloods was examined with the serum from patient 2. (Group A as well as group O bloods could be tested with the latter serum as it contained no α agglutinins.) Among a total of 101 individuals (not including the patients or donors of our two transfusion cases) 14 persons were encountered whose bloods did not agglutinate in the anti-Rh sera. This incidence of Rh— bloods (about 1 in 7) closely approximates that previously reported by Landsteiner and Wiener.

Our findings presented above confirm the occurrence of hemolytic reactions after transfusions of blood of the proper group, due to agglutinogens unrelated to the four blood groups. One may also consider that such incompatibilities might be detected before-hand by tests made at low temperatures. In this connection, a case seen by one of us several years ago is of interest.

Case 3. The patient was a female child, 4½ years of age, when first referred for blood transfusion by Dr. S. Katz in 1935. The patient first became ill during the winter of 1933 while in Florida, where she is said to have been handled and kissed by a nurse recuperating from acute rheumatic fever. The patient was taken home to Brooklyn where she ran an intermittent and remittent fever. During this illness, the patient also complained of pain and swelling of her thumb. She was treated at the Jewish Hospital for a time, where she was given a blood transfusion without any untoward reaction. Agglutination tests for typhoid, paratyphoid, etc. were negative. The patient recovered 16 weeks after the onset of the illness, following a tonsillectomy.

She again became ill at the end of November 1934, with remittent and intermittent fever ranging as high as 104° F. This was accompanied by migratory joint pains. In January 1935, because of a developing anemia, the patient, who belonged to group A, was given a transfusion of 180 c.c. of blood from a group A donor without

any untoward reaction. (The bloods were also shown to be compatible by the usual open slide technic.) On February 14, 1935, the patient was given a second transfusion of 100 c.c. of blood from the same donor (after re-grouping and cross-matching the bloods). One hour after this transfusion, the patient had a severe chill and the temperature rose to 106° F. As reëxamination of the bloods of patient and donor again corroborated the previous results, this was interpreted as a non-specific reaction, the clinical condition being blamed as a contributing factor. After the transfusion the patient's temperature remained normal for two days, then intermittent fever ranging up to 105° F. and 106° F. recurred and continued for two weeks. As the patient's hemoglobin was dropping and her clinical condition continued downhill, a third transfusion of 150 c.c. of blood was given from the same donor. This was followed by a sharp chill, rise in temperature to 107° F. and hemoglobinuria. The patient developed a hemorrhagic tendency, and blood oozed from all puncture wounds, including that of the transfusion, and from the mucous membranes. Another transfusion seemed urgently needed, but since retests again proved patient and donor to belong to group A, and the cross-matching tests were again negative, this idea was abandoned, there being no assurance that a different donor's blood would not also be incompatible. (Indeed additional tests even showed that the bloods of recipient and donor both belonged to subgroup A_1 and type MN, so that neither the subgroups nor the properties M and N could be implicated as the cause of the reaction.) The oozing of blood continued and the patient died two days later from exsanguination.

In the case just described, it seems certain that the hemolytic reaction must have been due to the appearance in the patient's plasma of immune isoantibodies for the donor's blood cells. It is possible that agglutinins might have been demonstrable in the recipient's serum, if the sensitive technic outlined in the present paper had been used; namely, incubation of the mixtures of serum and cells in the refrigerator, with or without centrifugation. Possibly the cases reported by DeGowin and Baldridge,[9] Johnson and Conway,[13] and Goldring and Graef,[10] etc., could have been explained in a similar way. However, there is evidence that not all intra-group transfusion reactions can be traced to the formation of Rh antibodies in a Rh-individual. For example, in Zacho's case,[41, 42] the agglutination reactions given by the patient's serum were of highest titer at 37° C. and weakest at low temperatures. Aside from this peculiarity of the antibody, the difference in the frequency of bloods containing the agglutinable factor proves that the property Rh played no part in the reaction. The appearance following a transfusion of an immune isoagglutinin with properties similar to those of Zacho's case has been reported by Neter.[27] With regard to the transfusion reaction reported by Mandelbaum,[23] the blood of the patient was retested by us and found to be Rh positive. Accordingly the property Rh cannot be blamed for that reaction either. In the case reported by Levine and Stetson,[22] the incidence of bloods agglutinable by the patient's serum (based on 104 tests) was about 80 per cent, which is not significantly different from the frequency of Rh plus blood (about 85 per cent), but the antibodies gave just as intense reactions at 37° C. as at low temperatures. Whether or not the agglutinogen Rh was the responsible factor in the two cases reported by Culbertson and Ratcliffe [6] or in the cases reported by Bauer [2] cannot be decided from the data given in their papers. As to Mosonyi's report [26] of a hemolytic reaction fol-

lowing repeated transfusions of group B blood to a group B patient, the writer's conclusion that the reaction was due to the formation of immune isoagglutinins specific for group B blood is not intelligible to the present authors.

In addition to those cases where hemolytic reactions followed repeated transfusions of blood of the homologous group, there are a number of reports of intra-group hemolytic reactions in patients who had never received a previous blood transfusion, or where the previous transfusion had been given so long ago (several years) that they could hardly be blamed for the reaction. Such instances have been reported by Zacho,[41] Parr and Krischner,[29] Culberston and Ratcliffe,[6] McCandless,[25] Johnson and Conway,[13] Smith and Haman,[34] Mandelbaum [23] and Levine and Stetson.[22] Remarkably enough in all of these cases except the one reported by McCandless * the patients were women who had recently given birth or had had a miscarriage.† Culbertson and Ratcliffe remarked concerning this coincidence in their two cases but did not attempt any explanation. In the case reported by Levine and Stetson, the patient, who had just had a stillbirth, was transfused with blood from her husband and a hemolytic reaction resulted. These authors suggest that the fetus inherited an antigenic substance from the father which was lacking in the mother, and the latter became immunized to the antigen after carrying the fetus for a long time after it had died in utero. In support of their interpretation that the agglutinin found in their patient's serum was an immune antibody rather than a natural one, Levine and Stetson cite the gradual drop in its titer and its eventual complete disappearance several months after the transfusion. In the other instances referred to above, a similar explanation may hold, though the individual antigenic differences responsible need not be the same in every case.

In support of this idea can be cited the report by Jonsson,[14] who found the average titer of the isohemolysins α and β to be higher than normal in women who had recently given birth, and who attributes this phenomenon to the specific stimulation provided in instances of heterospecific pregnancy. If the presence of a group A or group B fetus in a group O mother can cause a rise in titer of the isoantibodies α and β, respectively, it does not seem improbable, that, for example, a Rh— woman carrying a Rh+ fetus might

* With regard to the McCandless case, this is actually not an instance of an intragroup hemolytic reaction, since retests of the donor's blood by Hoxworth [12] have shown that the donor actually belongs to group A (subgroup A_2) not to group O as stated in the original case report. The case reported by Von Deesten and Cosgrove [36] of renal insufficiency following a blood transfusion is not a true hemolytic reaction since the hemoglobin rose from 70 per cent before the transfusion to 87 per cent after the transfusion. The rise in hemoglobin resulting from the transfusion corresponds closely with the predicted rise from a transfusion of 750 c.c. of blood, which was the amount given. If hemolysis had occurred there should have been no rise in hemoglobin. Moreover, the symptoms were not typical of a transfusion reaction and could be more logically attributed to the slight kink of the right ureter detected subsequently by pyelogram.

Incidentally, Thalhimer's case [35] frequently cited as an example of the danger of repeated blood transfusions from the same donor is not an example of an intragroup reaction, since the donor belongs to group B and the patient to group O.

† While this paper was in press, our attention was called to another instance of intragroup incompatibility reported by Pondman,[43] occurring in a postpartum case.

react by producing Rh antibodies. However, the paucity of reports of intra-group hemolytic reactions even in postpartum cases indicates that this phenomenon must be rare. Possibly in normal pregnancy the placenta offers a barrier to the passage of antigens from fetus to mother, and, in addition, as pointed out above, because of constitutional differences not all individuals will respond to the foreign antigens by producing specific antibodies.

An important question is what bearing other known individual differences of human blood, namely, those dependent on differences in the agglutinogen A (A_1 and A_2) and on the agglutinogens M, N and P, have on the occurrence of intra-group transfusion reactions. With respect to the subgroups of groups A and AB, it has been shown by Landsteiner and Levine [18] that a small percentage of individuals belonging to these groups have in their plasma irregular agglutinins acting on blood of the opposite subgroup. Some writers [3, 7] assert that differences in the subgroups can cause hemolytic reactions and warn that only donors of the homologous subgroup be used for transfusions. As a matter of fact no case has yet been reported where the subgroups were conclusively proved to be responsible for a serious reaction. In our own experience with over 3,000 transfusions [39] the incidence of even minor reactions among patients of group A when donors are selected without regard to the subgroups is not significantly higher than among patients in groups O and B, the blood cells of the donor persisting in the patient's circulation whether donor and recipient belong to the same or different subgroups. Similar has been the experience of Hoxworth [12] in a series of 2950 transfusions. As is illustrated by case 2, in hemolytic transfusion reactions, even if it is found that patient and donor are not in the same subgroup this does not prove the difference in subgroups to be responsible. To the best knowledge of the writers, no report has appeared in the literature which proves that agglutinogen A, can be antigenic for A_2 persons, or vice versa, but recently two such cases have come to our personal attention.[39] One patient (of subgroup A_2) had received repeated transfusions of A_1 blood; the other (also of subgroup A_2) was a postpartum case. Both had α agglutinins in their sera of titer 16 at room temperature. Accordingly, the most practical procedure, and the one followed by us, is to disregard the subgroups when selecting donors for transfusion except in the infrequent cases where the patient's plasma contains the irregular isoagglutinins α_1 or α_2 and then to use donors of the homologous subgroup. Such instances can be detected by the usual cross-matching tests.

With regard to the agglutinogens M and N, the situation is similar. Despite the performance of hundreds of thousands of transfusions every year, in which donors are selected without regard to their M–N types, not a single hemolytic reaction can be traced to this source. The report by Martinet [24] that he observed the formation of specific hemolysins for M and N following transfusions is unconvincing, and in the present authors' experience repeated injections of type M blood into type N individuals or vice-versa has not stimulated the production of isoantibodies for M or N. Evi-

dently, therefore, these agglutinogens, unlike A and B, are not antigenic, or at most very feebly antigenic, for human beings. Accordingly, the prominence given them by certain writers [31] as a possible source of hemolytic reactions after repeated transfusion is not warranted, though the possibility that such cases may ultimately be found cannot be excluded. Only three cases (among hundreds of thousands of persons tested) are known of human beings with natural anti-M isoagglutinins, none having been encountered to date with anti-N agglutinins. In patients with such isoagglutinins, it would of course be wise to take the agglutinogens M and N into account when selecting the blood donor.

At least one case is known where the injection of blood containing agglutinogen P into an individual lacking the agglutinogen stimulated the formation of isoantibodies for P. In this case, seen by Dr. S. H. Polayes, there was difficulty in finding a compatible donor for a patient of group A, since her serum agglutinated most other bloods of group A. This patient had had a previous transfusion without untoward reaction from a group A donor whose cells were now also agglutinated by her serum. The patient's blood was referred to one of us [39] for study and it was found that the abnormal reactions of its serum corresponded with the agglutinogen P. For this patient, accordingly, only blood of group A(P—) would be suitable for transfusion.

With regard to the rôle played by irregular agglutinins in general in hemolytic reactions, it may be said that they show marked differences as to their significance in transfusions. In a number of instances [18, 19] where patients were transfused with blood acted on by atypical agglutinins in their sera, no untoward symptoms resulted, although the in vitro reactions were at times as strong as those described here. This indicates the existence of some as yet undescribed qualitative difference among the various irregular isoantibodies.

No evidence exists that pseudoagglutination (or pronounced rouleaux-formation) can cause untoward transfusion reactions. Also, in the authors' experience autoagglutinins have not caused hemolytic reactions. (In patients with autoagglutinins, however, we take care to keep the blood at body temperature during its infusion, while ordinarily we are content with blood at room temperature.) Indeed, injudicious attempts to warm up the blood as a routine are dangerous, and in at least one case the injection of blood damaged by overheating gave rise to a fatal hemolytic reaction.[1] Another non-specific cause of severe or even fatal hemolytic transfusion reactions that has come to the fore in recent years is the use of pr -ved blood stored for too long periods of time before injection. As is pointed out elsewhere,[33, 40] the safe time limit for the storage of blood for transfusion is between five and 10 days.

Discussion

The danger of intra-group hemolytic reactions has been shown to be greatest in patients receiving repeated blood transfusions and in postpartum

cases. With regard to the warning [15] not to use the same donor for patients receiving repeated transfusions, our findings show that this measure is not sufficient to exclude transfusion reactions, since the antigens responsible may occur in a considerable percentage of individuals. In fact, the patients in cases 1 and 2 would have been safer with repeated transfusions from a single Rh— donor. With regard to the postpartum patients who had hemolytic reactions following transfusions of blood of the proper group, though never transfused previously, these should belong to the same category as the patients immunized by repeated transfusions, if the theory suggested is correct; namely, that the patients became immunized while the fetus was in utero to antigens shared by fetus and blood donor (usually the husband) but absent from the patient's body. Incidentally, some writers consider leukemia and hemolytic icterus contraindications to blood transfusion, as hemolytic reactions have been observed following transfusions of apparently compatible blood in these diseases. The formation of immune isoantibodies seems the most plausible explanation for these observations, because such patients are usually given many blood transfusions.

With regard to the prophylaxis of intra-group hemolytic reactions, no single in vitro technic will cover every exigency, as while most of the irregular isoagglutinins act best at low temperatures, others have been found that react more strongly at body temperatures. However, the following technic of cross-matching is advised in addition to the usual grouping and cross-matching tests, as it will anticipate most reactions of this sort.

1. Two drops of patient's serum, preferably separated from the clot at refrigerator temperature, are mixed with one drop of donor's cell suspension in a small test tube.

2. In a second tube a similar mixture of patient's serum and patient's cells is set up.

The tubes are placed in ice-water for 5 minutes, then centrifuged while still cold and the mixtures are gently shaken. The reactions are read both macroscopically and microscopically. If neither tube shows a reaction, the donor is compatible. If both show a reaction, we are dealing with an autoagglutinin and the donor probably can be used without danger. If tube 1 shows agglutination and tube 2 does not, the donor is incompatible and others must be tested in order to find a suitable one.

In any event, in patients receiving repeated transfusions and in postpartum cases the serological test should be supplemented by a biological test,[28] if time permits. In citrate transfusions it is a simple matter to inject the first 50 or 100 c.c. of blood very slowly in order to determine whether a reaction will occur. If a chill * results, the infusion should be stopped and another donor tried. This procedure would probably prevent any serious consequences since 100 c.c. of incompatible blood are hardly enough to cause a fatal reaction. In a series of 15 hemolytic reactions with 10 fatalities analysed by Bordley, all patients receiving less than 350 c.c. of blood recovered.

Our findings are also of interest since they demonstrate by another method the large number of individual differences in human blood. With

* A chill caused by a blood transfusion usually begins within an hour.

the agglutinogens A_1, A_2, B, M, N, P and Rh alone as many as 72 different types of human blood are readily distinguished. Also remarkable is the correspondence between the reactions of the sera of our two patients and the anti-rhesus immune sera prepared by Landsteiner and Wiener.

Summary

Three cases are reported in which repeated transfusions of blood of the proper group gave rise to hemolytic reactions, two of the three reactions resulting in the death of the patient.

In two cases there was noted the appearance in the patient's serum of an isoagglutinin designated as anti-Rh. This is explained as the immune response to the injection of Rh+ blood into Rh— individuals, the blood group playing no rôle. Following the appearance of the anti-Rh agglutinins the transfusion of Rh+ blood gave rise to hemolytic reactions. Remarkably the reactions of the anti-Rh sera corresponded with those of immune rabbit sera prepared by Landsteiner and Wiener by the injection of rhesus blood. The frequency distribution of agglutinogen Rh in the general population is approximately 85 per cent Rh+ and 15 per cent Rh—.

Our cases were compared with others reported in the literature and various similarities and differences pointed out. A hypothesis is offered to explain the occurrence also of hemolytic intra-group reactions in certain individuals who had not received previous blood transfusions. The rôle played by the properties A_1, A_2, M, N and P in transfusion reactions is discussed. Methods are suggested for the prevention of occurrence of intra-group hemolytic reactions.

Addendum

While this article was in press, an additional case of intragroup incompatibility, based on individual blood differences with respect to the property Rh, was observed. The history of this case is as follows:

Case Report. The patient was a woman, 58 years of age, admitted to the private service of Dr. Frank Teller at the Jewish Hospital of Brooklyn, with the diagnosis of diabetic gangrene of the toes of one foot. Amputation was performed, and following the operation, the patient's condition was poor. A transfusion of 500 c.c. of citrated, group A, compatible blood was given by the gravity method. Despite the transfusion, the hemoglobin dropped from 78 to 70 per cent; the red blood cell count from 3.95 million to 3.14 million per cu. mm. Following this transfusion, which was given on April 18, 1940, there was no detectable untoward reaction. On April 25, a second transfusion was performed; this time 300 c.c. of group O blood were given. One hour after the transfusion, the patient had a severe chill lasting 30 minutes, and there was an abrupt rise in temperature. Moreover, again there was no appreciable improvement in the hemoglobin or red count, and it was decided to investigate the cause of this transfusion reaction in greater detail.

The grouping tests revealed:

Blood of	Group	Subgroup	Type
Patient	A	A_2	M
1st donor (patient's son)	A	A_2	MN
2d donor (professional)	O	—	M

It is clear that the fate of the blood received at the first transfusion could be determined by testing the patient's blood with anti-N serum; the fate of the blood received at the second transfusion by tests with anti-A serum. Tests made on a sample of blood drawn four days after the second transfusion showed that all the blood received at the two transfusions had been eliminated from the circulation, while transfused cells ordinarily survive for periods up to three and four months. This indicated the existence of some incompatibility between the blood of the patient and those of the two donors. Tests were then set up by the centrifuge method in the cold, and it was found that while no agglutination occurred in mixtures of the patient's serum with her own cells, strong clumping was evident in the tubes containing the bloods of the donors. This phenomenon was evidently connected in some way with the transfusion reaction, and supplied the key to the explanation for the rapid disappearance of the donors' cells from the patient's circulation. A series of blood specimens from individuals who had previously been tested for the property Rh was then tested with the patient's serum, and the results proved that we were dealing once more with an incompatibility reaction based on the property Rh.

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THE CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE AND IN ORGANIC HEART DISEASE*

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THE mechanism of heart failure is still the subject of investigation. In recent years, however, observations have been made which lead to a clearer understanding of its pathological physiology. In 1932 Stewart and Cohn [1] published data showing that in human beings "The volume output of blood per minute from the heart which is in failure is diminished and its size larger than when it is in a state of compensation." In addition, there were certain observations relating to dogs pointing to the same conclusions.[2] Since then Stewart and his associates [3] have made further investigations of patients suffering from congestive heart failure which contributed to the same notion. We have continued our studies of this subject and now bring together our data relating to it.

In our observations we have related certain objective measurements of the circulation to the several functional states which can be recognized clinically in patients suffering from cardiac disease. For instance, certain patients exhibited signs of organic heart disease but had never experienced congestive failure; in others, observations were made in the presence of congestive heart failure; in others, after recovery from failure; and in another group studies were made both during and after recovery from failure. Representative patients of each of the four most common etiological rubrics, namely rheumatic fever, arteriosclerosis, hypertension and syphilis, were observed, those exhibiting normal sinus mechanism as well as those in whom auricular fibrillation prevailed.

METHODS

All observations were made in the morning while the patients were in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken, as recommended by Grollman [4] in his book entitled "The Cardiac Output of Man in Health and Disease," and as further elaborated by Grollman, Friedman, Clark and Harrison.[5] During this measurement the patient sat in a steamer chair (at an angle of 135 degrees) with the legs extended. Each patient was made familiar with and trained to carry out the procedures beforehand. While

* Received for publication October 3, 1939.
Read in part at the New York Meeting of the American College of Physicians April 6, 1938.
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he was resting quietly, the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-air-oxygen mixture was rebreathed. The amount of gas in the "rebreathing bag" was adjusted to the amount the patient could breathe satisfactorily. Three samples of gas were obtained during each period of rebreathing for estimation of the arteriovenous oxygen difference. Three periods of rebreathing were carried out to make certain that mixing was secured; one, two or all sets were analyzed. The arteriovenous oxygen differences in those in which checks were secured were averaged. Satisfactory checks can be secured by this method in the grade of heart failure which we studied (figure 1). Shortly

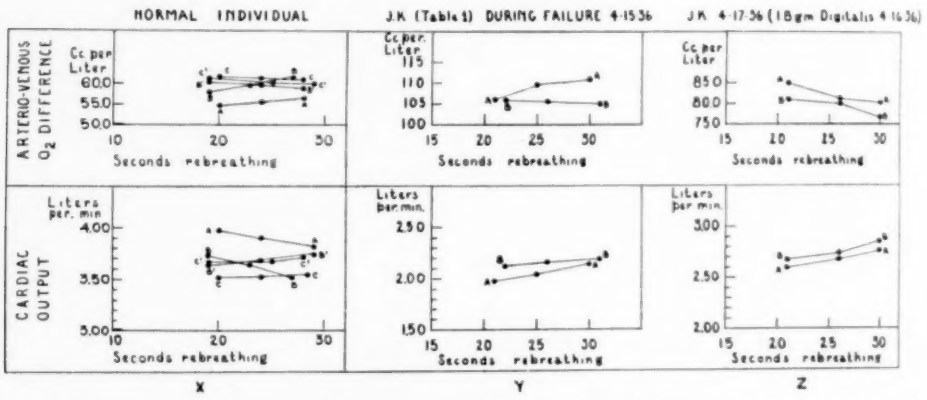


FIG. 1. In this figure are shown data relating to the application of the Grollman 3 sample technic to patients suffering from heart failure. In figure 1*X* are data obtained from a normal individual for comparison. Rebreathings *A*, *B* and *C* were secured in succession on 4–8–35, B^1 on 4–9–35 and C^1 on 4–10–35. The first point on each curve represents the arteriovenous oxygen difference calculated from the first and second samples of a rebreathing, and the third, that is to say the last point, from the second and third samples. The point in the middle is the average of the two. The cardiac outputs correspond to these arteriovenous oxygen differences. It is apparent that the arteriovenous oxygen differences and cardiac outputs agree, not only on the same day but also on successive days. In figure 1*Y* are plotted in a similar fashion data of J. K. (table 1) during heart failure. Satisfactory checks were secured. In figure 1*Z* are plotted data of J. K. (not given in table 1) secured on 4–17–36 after the patient had been given 1.8 gm. digitalis and clinical improvement had occurred. Checks were again obtained. The arteriovenous oxygen differences have decreased and the cardiac outputs increased as compared with data of 4–15–36.

after the rebreathings, the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause the vital capacity was measured, and the height and the weight were recorded. Then the patient rested again, this time by lying down. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, an electrocardiogram was taken, the arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured; finally, the basal state still being maintained, a roentgenogram of the heart was made at a distance of 2 meters.

The arm to tongue circulation time was estimated by the use of decholin sodium [6]; 5 c.c. of a 20 per cent solution were injected rapidly (one to two

seconds) through an 18 gage needle into an antecubital vein while the patient was lying quietly in a supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste. The injection time was also recorded; since, however, the response may come with a minimal amount of the drug, the time which we used was measured from the start rather than from the conclusion of the injection.

The venous pressure was measured by the direct method,[7] a large antecubital vein being used and the arm being placed on a level with the right auricle. The apparatus consisted of an L tube of glass attached to a three way stopcock, a syringe and an 18 gage needle. The apparatus was filled with a sterile normal solution of sodium chloride, venipuncture was performed, and the direct pressure readings were recorded. Normal pressures with this apparatus range from 4 to 10 cm. of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the cardiac silhouette were taken with the patient in the standing position, during full inspiration, at a distance of 2 meters.* Measurements of the cardiac area were carried out by the technic of Levy,[8] and estimations of volume were made as recommended by Bardeen.[9]

The work of the left ventricle per beat was calculated by making use of the formula[10]: $W = QR + (wV^2/2g)$, in which W equals the work done per beat; Q equals the volume of blood expelled per beat; R equals the mean arterial blood pressure in millimeters of mercury times 13.6; V equals the velocity of blood in the aorta; w equals the weight of the blood, and g equals the acceleration due to gravity. The last part of the formula, $wV^2/2g$, was omitted.[11]

Plan of Observations

Observations were made of certain patients who suffered from organic heart disease, but who had never experienced heart failure, and of patients who had recovered from heart failure at some time in the past. Certain of these patients were admitted to the hospital in the afternoon and underwent training for the procedures which were to take place in a basal state the following morning. Others of them, if they lived in the neighborhood, came to the hospital on one occasion for training, and rode in a taxicab to the hospital without breakfast on the morning the observations were to be made; they rested one hour after their arrival. Those patients who were studied both during failure and after recovery from failure, as well as those in the hospital concerning whom data were collected only during failure or only after recovery from failure, were all treated in a uniform fashion[3, 12] with

* The authors are deeply indebted to the Roentgen-Ray Department of the New York Hospital for their coöperation in this investigation.

TABLE I

Data Relating to Patients Suffering from Congestive Heart Failure

Name	Age	Sex	Date	Oxygen Consumption	Arterio-venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm. Hg
Hypertensive Group										
A. F.	38	M	1/ 4/36	286	110.9	2.58	1.59	94	29	211/145
M. R.	68	M	1/21/36	274	117.6	2.33	1.27	120	20	170/94
M. H.	53	M	11/23/35	280	98.3	2.85	1.66	82	35	153/110
F. G.	51	M	3/ 5/36	263	81.4	3.23	1.62	68	47	160/110
L. B.	64	M	2/29/36	249	82.8	3.01	1.70	100	30	200/114
Arteriosclerotic Group										
C. K.	48	M	11/13/35	212	88.9	2.38	1.50	114	21	97/78
F. St. J.	73	M	9/25/35	245	94.4	2.60	1.37	60	43	150/90
Luetic Group										
J. K.	55	M	4/15/36	220	107.5	2.05	1.26	98	21	156/40
F. K.	61	M	2/28/35	240	83.1	2.89	1.45	119	24	174–160/110
Rheumatic Group										
S. S.	32	M	2/19/36	245	115.3	2.13	1.23	70	30	114/76
W. B.	32	F	4/28/36	207	106.3	1.95	1.32	80	24	110/80
W. H.	24	M	9/23/35	263	92.8	2.83	1.93	110	28	94/70
C. S.	29	F	4/24/36	185	113.8	1.63	1.07	98	17	102/82
J. G.	28	M	3/13/35	272	95.2	2.86	1.82	102	28	150–130/90
L. C.	30	F	3/ 4/35	222	96.8	2.29	1.38	100	23	120–110/74
M. C.	53	F	1/28/36	207	102.9	2.01	1.25	100	20	170/100
G. MacF.	57	M	2/25/36	189	84.2	2.24	1.47	64	27	110/90
J. M.	37	M	2/27/34	203	100.5	2.02	1.17	76	27	140/80
M. P.	41	F	4/30/34	180	90.6	1.98	1.28	124	16	112/70
B. D. §	49	F	3/12/36	180	82.0	2.20	1.51	46	48	122/70
S. C. §	39	F	3/23/36	166	67.8	2.45	1.74	64	38	108/66
A. G.	34	M	4/20/35	317	147.8	2.14	1.17	160	13	94/64
M. P.	40	F	11/20/37	205	101.9	2.01	1.16	94	22	110/80
			1/ 5/38	171	91.9	1.86	1.21	78	24	90/65
A. C.	32	M	3/27/35	278	119.8	2.32	1.28	150	15	94/56

* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh. = rheumatic fever
Unk. = unknown
Hypt. = hypertension
Artscl. = arteriosclerosis
R-I-V-HB = right intra-ventricular heart block
M.S. = mitral stenosis
M.I. = mitral insufficiency
A.S. = aortic stenosis
A.I. = aortic insufficiency
Enl.Ht. = enlargement of the heart

‡ 0, +, ±, ↓, ↑, = absent, present, doubtful, decreased, increased, respectively.

§ This patient, unlike the others in this group, was under the influence of digitalis when the special studies of the circulation were made.

TABLE I (*Continued*)

Data Relating to Patients Suffering from Congestive Heart Failure

Left Ventricular Work	Circulation Time	Venous Pressure	Vital Capacity	Cardiac Area	Cardiac Volume *	Diagnosis †	Signs ‡						Rhythm
							Dyspnea	Cyanosis	Rales	Liver	Edema	Fluid in chest	
gm.m./ per beat	sec.	cm.	c.c.	sq.cm.	c.c.								
						Hypertensive Group							
76.0	22.3	21.0	1400	167.2	1044	Hypt.; Enl. Ht.	+	0	+	+	0	0	N.R.
36.0	25.9	21.3	1600	172.3	1091	Artscl.; Enl.Ht.; Hypt.	+	±	+	+	+	0	N.R.
63.0	35.1	10.7	1900	218.2	1555	Artscl.; Hypt.; Enl.Ht.; R-I-V-HB	+	+	+	+	0	+	N.R.
86.0	50.0	21.5	2700	234.2	1730	Hypt.; Enl.Ht.	+	+	+	+	+	0	N.R.
66.0	15.8	18.6	1300	141.1	809	Artscl.; Hypt.; Enl.Ht.	+	+	+	+	±	0	N.R.
						Arteriosclerotic Group							
25.0	30.0	19.0	2300	176.2	1130	Artscl.; Enl.Ht.	+	+	0	↑	+	0	N.R.
70.2	55.0	14.8	1200	166.6	1039	Artscl.; Enl.Ht.	+	+	+	+	+	0	A.F.
						Luetic Group							
28.0	25.8	18.3	1500	204.5	1420	Syphilis; A.I.; Enl.Ht.	+	+	+	+	+	+	N.R.
44.6	20.1	17.3	2200	198.0	1346	Aneurysm; Enl.Ht.	+	+	+	0	+	0	N.R.
						Rheumatic Group							
39.0	42.6	18.1	3200	215.6	1528	Rh.; M.S. and M.I.; Enl.Ht.	0	+	+	+	0	0	N.R.
31.0	27.0	17.0	1500	194.2	1317	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	±	N.R.
29.0	26.6	5.8	2700	220.5	1579	Rh.; M.S. and M.I.; Enl.Ht.	+	+	0	+	0	0	N.R.
21.3	36.4	24.8	1700	206.3	1430	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	0	N.R.
43.8	25.4	23.2	2600	164.3	1019	Unk.; M.S. and M.I.; Enl.Ht.	+	+	+	+	+	0	A.F.
31.3	22.5	6.6	2750	202.9	1399	Rh.; M.S. and M.I.; Enl.Ht.	+	+	0	+	+	0	A.F.
36.7	34.0	11.4	1550	194.2	1320	Rh.; M.S. and M.I.; Hypt.; Enl.Ht.	0	+	+	+	+	+	A.F.
36.7	24.0	7.9	1750	158.6	965	Rh.; M.S. and M.I.; Enl.Ht.	0	+	+	+	0	0	A.F.
40.4			2700	218.0	1554	Rh.; M.S. and M.I.; Enl.Ht.	+	+	+	+	0	0	A.F.
19.8			2080	173.2	1102	Rh.; M.S. and M.I.; Enl.Ht.	0	0	+	+	0	0	A.F.
62.6	25.4	10.3	2000	148.6	876	Unk.; M.S. and M.I.; Enl.Ht.	+	+	0	+	0	0	A.F.
45.0	20.2	15.8	2000	153.6	918	Unk.; M.S. and M.I.; Enl.Ht.	+	+	0	+	+	0	A.F.
14.4	33.4	22.7	2700	258.6	2008	M.S. and M.I.; Enl.Ht.	0	+	0	+	0	0	A.F.
28.4	27.5	25.0	1400	180.9	1172	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.	0	+	+	+	+	+	N.R.
25.5	24.7	13.9	1900	173.3	1120		0	0	+	+	0	0	N.R.
15.3	28.0	7.2	3500	171.9	1090	M.S.; M.I.; A.I.; Enl.Ht.	+	+	+	+	0	0	A.F.

respect to use of fixed fluid and limited salt intake, and to the use of digitalis in a uniform manner.* [3, 12] In estimation of the average values, those in whom the diagnosis was rheumatic heart disease make up a group, and those in the hypertensive luetic and arteriosclerotic rubrics have been considered together as a miscellaneous group, and finally the average of all groups combined has been taken.

Data are recorded in tables 1, 2, 3 and 4.

* They had been given 1.6 to 1.8 gm. of digitalis (New York Heart Association) within 24 hours as the digitalizing amount and on the average 0.2 gm. a day as the maintenance amount.[3, 12] The method of treatment is not expanded because observations were made during failure and after recovery from failure in order to compare the two states.

TABLE II

Mean Values of Measurements of Normal Individuals * and Patients Suffering from Heart Disease (tables 1, 3, and 4)

Classification†	Arterio-Venous Oxygen Difference (c.c.)	Cardiac Index (liters per minute)	Stroke Volume (c.c.)	Venous Pressure (cm. normal saline)	Circulation Time (sec.)
Normal Individuals (16 observations on 11 subjects)	61.5	2.09	59	10.1	14.4
Heart Disease before Failure (46 observations on 39 patients)					
Rh.	73.0	1.83	42	8.7	15.0
Hypt., Artscl., Syph.	64.4	2.05	50	6.2	16.6
Rh., Hypt., Artscl., Syph.	71.4	1.87	43	8.1	15.4
Heart Disease Recovered Failure (31 observations on 23 patients)					
Rh.	79.9	1.65	43	7.1	21.5
Hypt., Artscl., Syph.	72.6	1.88	44	7.5	26.2
Rh., Hypt., Artscl., Syph.	76.9	1.73	44	7.3	23.7
Heart Disease during Failure (25 observations on 24 patients)					
Rh.	100.0	1.37	25	15.0	28.4
Hypt., Artscl., Syph.	96.1	1.49	30	18.1	31.3
Rh., Hypt., Artscl., Syph.	99.0	1.42	27	16.2	29.6

* Data from Stewart, H. J. and Watson, R. F.[13]

† Rh. Hypt., Artscl., Syph. = Rheumatic fever, Hypertension, Arteriosclerosis, Syphilis, respectively.

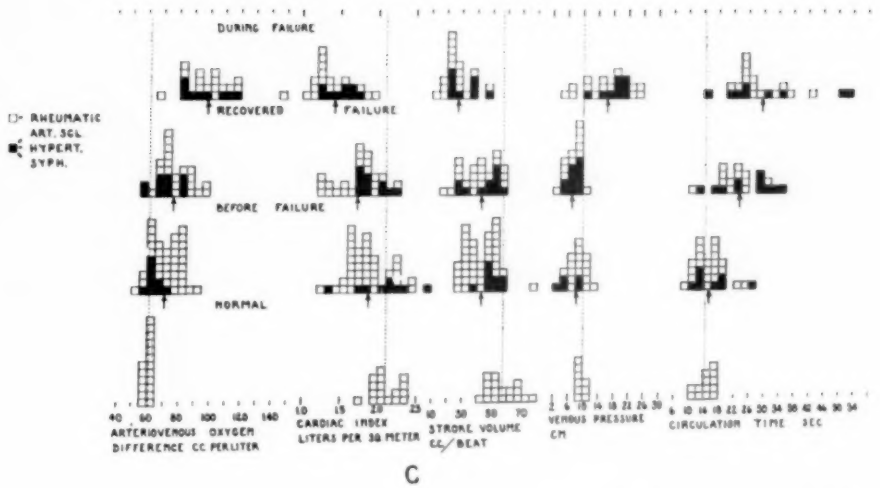
OBSERVATIONS MADE DURING HEART FAILURE

There are 25 observations on 24 patients belonging to four etiological groups, namely rheumatic, hypertensive, luetic, and arteriosclerotic (tables 1 and 2; figures 2 *a, b, c*). The average cardiac index ‡ for all etiological groups was reduced to 1.42 liters (2.09 liters in normal individuals), being 1.37 liters for the rheumatic group, and 1.49 liters for the miscellaneous group.

The average arteriovenous oxygen difference was increased to 99.0 c.c. for all groups, and was 100.0 c.c. and 96.1 c.c. when separated into rheumatic and miscellaneous rubrics (average normal, 61.5 c.c.).

‡ Cardiac index = cardiac output in liters per square meter of body surface.

FIG. 2. In this figure are plotted as frequency diagrams the data relating to measurements of the circulation in the group of normal individuals and in the heart disease groups (tables 1, 2, 3, and 4). In this figure, as well as in figure 3, each square is a unit and represents one measurement, and they are piled on top of one another when there is recurrence of that increment in that group. The increments are as follows: arteriovenous oxygen difference, 5 c.c.; cardiac index, 0.1 liter; stroke volume, 5 c.c.; venous pressure, 2 cm.; and circulation time, 2 seconds. The means of the normal group have been extended through the other groups by a dotted line. The mean of each group is indicated by the position of an arrow just below or above that particular group. Figure 2*a* refers to data of hypertensive, arteriosclerotic and syphilitic patients (miscellaneous group), before, during, and after recovery from heart failure; figure 2*b* refers in a similar fashion to rheumatic heart disease; and in figure 2*c* the data from figure 1*a* and 1*b* are combined.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FAILURE
BEFORE FAILURE
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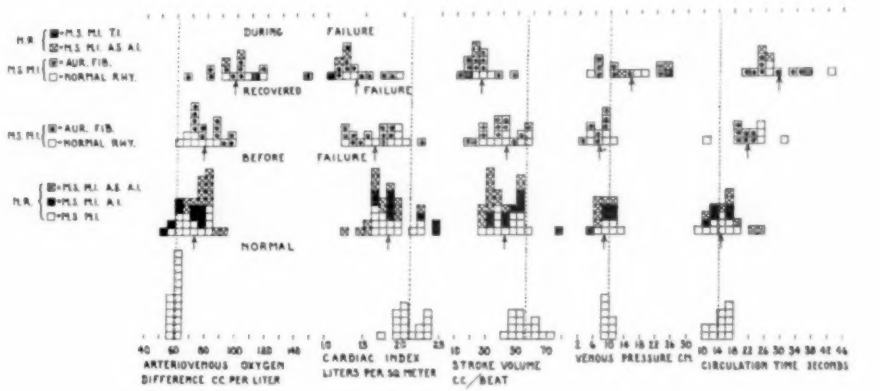
RHEUMATIC
ART. SCL.
HYPERT.
SYPH.
ARTERIOVENOUS OXYGEN DIFFERENCE CC PER LITER
CARDIAC INDEX LITERS PER SQ METER
STROKE VOLUME CC/BEAT
VENOUS PRESSURE CM
CIRCULATION TIME SEC

c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ARTERIOVENOUS OXYGEN DIFFERENCE CC PER LITER
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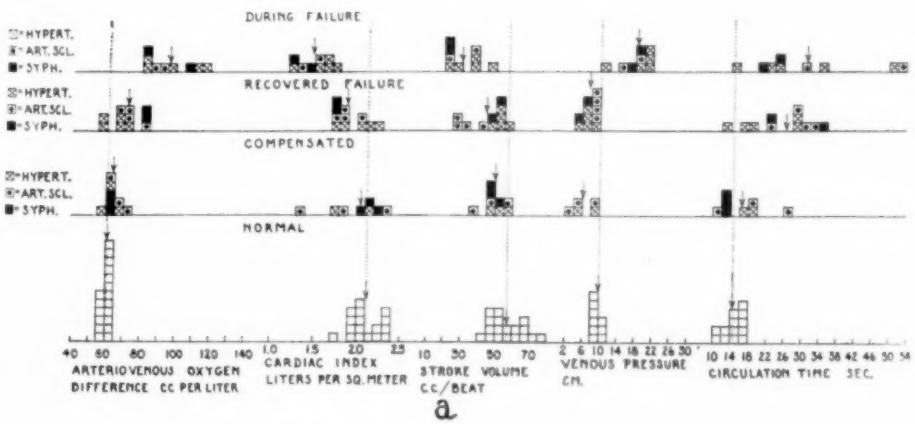
VENOUS PRESSURE CM
CIRCULATION TIME SECONDS

b


DURING FAILURE
HYPERT.
ART. SCL.
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RECOVERED FAILURE
COMPENSATED
NORMAL
ARTERIOVENOUS OXYGEN DIFFERENCE CC PER LITER
CARDIAC INDEX LITERS PER SQ. METER
STROKE VOLUME CC/BEAT
VENOUS PRESSURE CM.
CIRCULATION TIME SEC.

a

FIG. 2.

TABLE III

Data Relating to Patients Who Have Recovered from Heart Failure

Name	Age	Sex	Date	Oxygen Consumption	Arterio-venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm.Hg
Hypertensive Group										
A. F.	38	M	1/15/36	203	59.6	3.41	2.20	70	49	205/128
M. R.	38	M	1/29/36	207	68.0	3.04	1.70	60	50	170/80
M. H.	53	M	12/ 3/35	230	68.9	3.34	2.00	64	52	148/98
			12/11/35	220	70.9	3.10	1.84	60	52	148/95
L. B.	64	M	3/ 6/36	216	59.2	3.65	2.11	66	55	212/100
Arteriosclerotic Group										
C. K.	48	M	10/25/35	218	69.6	3.13	2.02	112	28	106/74
			11/18/35	207	72.8	2.84	1.81	100	28	106/58
			11/21/35	209	73.9	2.83	1.85	96	30	104/80
F. St. J.	73	M	10/ 2/35	241	81.2	3.00	1.70	66	45	136–130/80
Luetic Group										
F. V.	50	M	3/ 3/36	235	83.9	2.80	1.71	54	52	166/54
W. E.	42	M	3/24/36	234	81.3	2.88	1.74	62	45	180/90
Rheumatic Group										
S. S.	32	M	2/24/36	236	74.3	3.20	1.90	58	55	105/58
W. B.	32	F	5/ 7/36	166	82.3	2.02	1.50	48	42	98/65
F. S.	24	M	4/13/35	195	64.6	3.02	1.91	72	42	106/66
M. R.	32	F	4/ 4/34	158	89.6	1.76	1.21	60	29	115/55
C. W.	25	M	12/ 7/35	290	73.4	4.00	2.03	70	57	102/54
			12/19/35	286	75.8	3.77	1.95	70	54	116/66
L. A.	24	F	5/11/34	179	68.6	2.61	1.64	48	37	95/60
			5/31/34	194	65.5	2.95	1.80	93	32	120/84
J. G.	28	M	3/25/35	247	74.1	3.33	2.22	60	56	134/65
J. G.	28	M	11/12/35	237	86.3	2.75	1.80	66	42	135/76
			11/16/35	226	86.2	2.61	1.70	50	52	152/76
L. C.	30	F	3/ 6/35	207	74.4	2.78	1.70	70	40	118–110/74
M. C.	53	F	2/14/36	193	77.8	2.48	1.55	70	35	150/70
G. MacF.	57	M	2/29/36	182	70.8	2.57	1.70	68	38	118/62
M. P.	41	F	5/10/34	159	74.3	2.14	1.40	59	36	100/70
M. R.	25	F	4/11/34	191	96.2	1.98	1.30	86	23	98/60
			4/20/34	180	98.2	1.83	1.20	106	17	98/60
J. W.	28	M	3/ 9/34	188	92.0	2.05	1.34	74	28	115/80
			3/12/34	171	88.0	1.95	1.27	69	29	115/80
A. C.	32	M	4/ 2/35	263	78.3	3.36	1.86	72	47	114/76

* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh = rheumatic fever
Unk. = unknown
Hypt. = hypertension
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M.S. = mitral stenosis
M.I. = mitral insufficiency
A.S. = aortic stenosis
A.I. = aortic insufficiency
Enl.Ht. = enlargement of the heart
Syph. = syphilis
R-I-V-HB = right intraventricular heart block

‡ 0, +, ±, ↓, ↑, = absent, present, doubtful, decreased, increased, respectively.

TABLE III (*Continued*)

Data Relating to Patients Who Have Recovered from Heart Failure

Left Ventricular Work	Circulation Time	Venous Pressure	Vital Capacity	Cardiac Area	Cardiac Volume *	Diagnosis †	Signs ‡						
							Dyspnea	Cyanosis	Râles	Liver	Edema	Fluid in chest	Rhythm
gm.m./ per beat	sec.	cm.	c.c.	sq.cm.	c.c.								
Hypertensive Group													
111.0	12.5	8.5	2450	128.3	703	Hypt.; Enl.Ht.	0	0	0	±	0	0	N.R.
85.0	19.2	7.9	2800	150.8	894	Artscl.; Enl.Ht.; Hypt.	0	0	0	0	0	0	N.R.
87.0	29.1	6.4	2850	196.0	1325	Artscl.; Hypt.; Enl.Ht.; R-I-V-HB	0	0	0	↓	0	0	N.R.
86.0	29.0	7.0	2950	196.7	1331		0	0	0	?	0	0	N.R.
116.0	16.4	5.0	1900	125.9	682	Artscl.; Hypt.; Enl.Ht.	±	0	+	0	0	0	N.R.
Arteriosclerotic Group													
34.0	22.7	9.4	2900	155.3	940	Artscl.; Enl.Ht.	0	±	0	+	0	0	N.R.
32.0	30.4	8.7	2800	160.4	972		0	0	0	±	0	0	N.R.
37.0	28.0	9.4	3050	172.1	1091		0	0	0	±	0	0	N.R.
65.5	33.0	8.0	1800	157.1	951	Artscl.; Enl.Ht.	↓	±	±	±	±	0	A.F.
Luetic Group													
77.8	35.5	5.0	3300	182.0	1185	Syph.; A.I.; Enl.Ht.	0	±	±	±	0	0	N.R.
84.5	22.0	6.1	2900	172.4	1094	Syph.; A.I.; Enl.Ht.; Aneurysm	0	+	0	0	0	0	N.R.
Rheumatic Group													
61.0	31.7	5.8	3450	172.9	1097	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	+	0	0	N.R.
47.0	24.0	5.3	2100	183.4	1198	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
49.0	11.5	9.5	4400	162.9	1005	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
34.0			2100	154.4	925	Unk.; M.S. and M.I.; Enl.Ht.	±	+	0	0	±	0	N.R.
60.5	24.0	10.5	3850	273.6	2185	Unk.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	N.R.
66.8	25.2	8.8	4100	273.2	2185		+	0	0	0	0	0	N.R.
39.2			2700	140.6	806	Rh.; M.S. and M.I.; Enl.Ht.	±	±	±	±	±	0	N.R.
44.4			2610	137.7	781		±	±	±	±	±	0	N.R.
76.2	19.5	8.1	3250	146.5	856	Unk.; M.S. and M.I.; Enl.Ht.	0	0	0	0	0	0	A.F.
60.5	19.9	9.1	2750	154.3	926	Unk.; M.S. and M.I.; Enl.Ht.	0	+	0	+	0	0	A.F.
80.6	22.1	6.3	2900	143.5	821		0	+	0	+	0	0	A.F.
53.9	20.2	6.4	2700	185.3	1218	Rh.; M.S. and M.I.; Enl.Ht.	0	0	0	±	0	0	A.F.
52.3	22.2	8.1	2000	168.7	1160	Rh.; M.S. and M.I.; Hypt.; Enl.Ht.	0	0	0	0	0	0	A.F.
46.5	19.7	2.9	1850	143.1	827	Rh.; M.S. and M.I.; Enl.Ht.	0	0	±	0	0	0	A.F.
41.6			2200	162.0	996	Rh.; M.S. and M.I.; Enl.Ht.	0	0	↓	↓	0	0	A.F.
24.7			2100	189.8	1271	Rh.; M.S. and M.I.; Enl.Ht.	±	±	±	±	±	0	A.F.
18.5			2310	194.4	1310		±	±	±	±	±	0	A.F.
37.3			2400			Unk.; M.S. and M.I.	±	±	±	±	±	0	A.F.
38.7			2270				±	±	±	±	±	0	A.F.
60.7	18.0	4.7	4350	154.9	932	M.S.; M.I.; A.I.; Enl.Ht.	0	0	0	0	0	0	A.F.

The average output per beat (stroke volume) was decreased to 27 c.c., being 25 c.c. and 30 c.c. respectively when separated into the rheumatic and miscellaneous groups (average normal, 59 c.c.).

The average venous pressure for all groups was increased to 16.2 cm., and was 15.0 cm. and 18.1 cm. respectively in the rheumatic and miscellaneous groups (normal value, 10.1 cm.).

The average circulation time was 29.6 sec., the average normal for this method being about 14.4 sec.

TABLE IV

Data Relating to Cardiac Patients Who Had Never Experienced Heart Failure

Name	Age	Sex	Date	Oxygen Consumption	Arterio-venous Oxygen Difference	Cardiac Output	Cardiac Output	Heart Rate	Stroke Volume	Arterial Pressure
				c.c. per min.	c.c.	l./min.	l./sq.m./min.	per min.	c.c.	mm.Hg
Hypertensive Group										
C. C.	44	F	12/ 5/34	270	56.9	4.74	2.69	80	59	234/150
F. E.	50	M	10/22/36	226	69.6	3.25	1.70	64	51	174/130
E. L.	22	M	2/14/34	244	63.1	3.87	2.10	85	46	180/112
Arteriosclerotic Group										
C. McA.	69	M	1/15/35	259	64.6	4.01	2.40	70	57	120/60
J. S.	58	M	10/29/35	160	72.9	2.20	1.38	58	38	122/82
H. C.	50	M	10/ 1/35	267	68.2	3.92	1.84	88	45	120/80
Luetic Group										
H. W.	48	M	10/15/34	227	64.1	3.54	2.02	74	48	118/50
			10/16/34	232	60.3	3.85	2.20	72	53	108/40
			10/17/34	222	60.1	3.69	2.10	74	49	118/46
Rheumatic Group										
J. M.	18	M	1/28/35	218	83.3	2.62	1.68	96	27	110/68
W. L.	20	M	9/29/34	220	76.4	2.88	1.67	74	39	110/80
J. T.	20	M	6/28/34	273	82.4	3.32	1.80	74	45	115/70
W. H.	21	M	2/21/34	240	71.7	3.34	1.65	88	38	122/90
A. G.	23	M	10/30/34	210	69.9	3.00	1.74	76	39	118/80
			11/12/34	214	69.7	3.06	1.79	76	40	118/74
			1/10/35	243	71.9	3.38	1.94	74	46	104/70
			3/28/35	222	61.4	3.62	2.10	74	50	110/70
J. M.	23	M	11/ 3/34	229	81.9	2.97	1.68	72	39	110/60
C. W.	23	M	3/25/36	255	65.2	3.91	2.27	68	57	132/78
A. M.	24	M	9/28/35	203	57.6	3.52	1.90	66	54	124/70
R. T.	29	F	3/14/36	218	61.1	3.57	2.23	66	54	110/58
F. M.	32	M	11/ 1/34	259	81.4	3.18	1.77	70	45	122/72
M. H.	39	F	3/28/34	170	63.7	2.67	1.81	80	33	108/70
A. D.	17	M	11/14/36	218	75.0	2.91	1.80	54	54	125/68
R. L.	21	M	4/ 6/35	234	70.9	3.30	1.89	74	45	120/64
P. H.	22	M	5/22/34	227	64.7	3.51	2.21	70	50	122/74
A. M.	23	F	2/14/35	203	62.7	3.24	1.87	74	44	112/56
A. B.	23	M	4/10/34	207	74.9	2.88	1.63	90	32	136/88
J. L.	25	M	4/19/34	238	77.8	3.06	1.82	100	31	100/62
F. R.	26	M	1/26/34	219	77.5	2.83	1.62	72	40	130/64
H. W.	29	M	1/ 4/35	238	57.9	4.18	2.43	80	52	128/60
H. C.	40	M	6/15/35	249	52.4	4.73	2.40	60	79	108/68
H. N.	14	M	2/ 6/34	232	86.4	2.68	1.93	94	29	138/32
E. C.	19	F	3/18/35	195	82.8	2.36	1.42	86	27	104/10
J. H.	20	M	4/11/34	253	80.8	3.12	1.75	80	39	166/50
			4/15/34	251	90.0	2.80	1.50	83	34	162/40
			4/18/34	234	81.9	2.86	1.60	84	34	152/40
E. P.	21	M	11/ 8/34	195	71.4	2.73	1.77	80	34	122/50
J. F.	25	F	5/18/35	122	65.9	1.85	1.25	70	26	104/50
J. C.	28	M	12/ 9/37	331	75.5	4.15	2.21	80	52	128/30
E. F.	29	M	6/22/34	253	84.7	2.99	1.90	94	32	130/30
J. O.	31	M	3/ 7/36	203	77.7	2.61	1.61	60	44	96/70
M. S.	33	M	6/ 6/34	235	67.8	3.47	1.97	64	54	108/60
I. G.	43	M	6/27/34	249	79.0	3.15	1.87	93	34	155/35
S. H.	45	M	1/ 3/35	218	81.5	2.67	1.57	84	32	86/72
M. C.	46	F	12/10/34	182	77.4	2.35	1.63	66	36	128/84

* The cardiac volume has been multiplied by the constant in Bardeen's formula.

† In this column the following abbreviations are used:

Rh. = rheumatic fever
Unk. = unknown
Hypt. = hypertension
M.S. = mitral stenosis
M.I. = mitral insufficiency
A.S. = aortic stenosis
A.I. = aortic insufficiency
Enl.Ht. = enlargement of the heart
sl. E.H. = slight enlargement of the heart
Artscl. = arteriosclerosis
I-V-HB = intraventricular heart block
R-I-V-HB = right intraventricular heart block
N.R. = normal rhythm
A.F. = auricular fibrillation

I, IIA, IIB, III, refer to functional classification (Criteria for the Classification and Diagnosis of Heart Disease, ed. 2, New York Tuberculosis and Health Association, New York, 1929).

‡ Roentgen-Rays not repeated on these days.

TABLE IV (*Continued*)

Data Relating to Cardiac Patients Who Had Never Experienced Heart Failure

Left Ventricular Work	Circulation Time	Venous Pressure	Vital Capacity	Cardiac Area	Cardiac Volume *	Diagnosis and Rhythm †
gm.m. per beat	sec.	cm.	c.c.	sq.cm.	c.c.	
			Hypertensive Group			
145.1	19.0	5.5	2600	176.3	1130	Hypt.; I-V-HB; N.R.
105.4	17.0	8.0	4450	137.0	774	Hypt; N.R.
91.3			5640	111.2	566	Hypt.; nephritis; N.R.
			Arteriosclerotic Group			
70.0	11.5	5.5	2700	107.7	546	M.I.; not Enl.Ht.; IIA; N.R.
53.0	27.0	3.7	2600	139.0	792	None; not Enl.Ht.; IIA; N.R.
61.2	18.5	8.3	3300	159.3	972	Artscl.; Enl.Ht.; IIA; A.F.
			Luetic Group			
55.0	13.2		4100			A.I.; Enl.Ht.; I; N.R.
53.0	13.8		4100	137.5	774	
55.0	12.8		4250	138.5	782	
			Rheumatic Group			
32.7	11.0	7.5	3500	111.2	566	Unk.; M.S. and M.I.; I; N.R.
50.4			3400	108.6	542	Rh.; M.S. and M.I.; IIA; N.R.
56.9			4900	114.7	594	Unk.; M.S. and M.I.; ? sl.E.H.; I; N.R.
54.7			4050	114.8	595	Rh.; M.S. and M.I.; I; N.R.
53.0	16.0		4200	144.0	832	Rh.; M.S. and M.I.; Enl.Ht.; I; N.R.
52.0	18.5		4300	141.9	811	
46.7	16.5	11.0	4200	137.7	781	
61.2	15.4	10.3	4200	136.8	772	
45.1	13.2		3700	128.2	701	Rh.; M.S. and M.I.; sl.E.H.; IIA; N.R.
81.4	14.4	8.6	4200	122.4	655	Rh.; M.S. and M.I.; ? sl.E.H.; I; N.R.
71.2	13.4	12.3	5000	137.7	781	Unk.; M.S. and M.I.; ? E.H.; IIA; N.R.
61.7	9.6	8.0	3000	111.9	553	Rh.; M.S. and M.I.; ? sl.E.H.; I or IIA; N.R.
59.4	14.0		4900	138.2	784	Rh.; M.S. and M.I.; IIA; N.R.
40.3			2690	130.9	724	Rh.; M.S. and M.I.; sl.E.H.; IIA; N.R.
71.2	16.0	5.4	4000	119.5	632	Unk.; M.S. and M.I.; A.I.; ? sl.E.H.; I; N.R.
56.0	17.2	10.5	4100	120.6	647	Rh.; M.I., M.S., and A.I.; Enl.Ht.; I; N.R.
66.6			3400	148.3	872	Rh.; M.S. and M.I.; A.I.; Enl.Ht.; IIA; N.R.
52.0	11.6	10.1	2900	97.6	470	Rh.; M.I., M.S., and A.I.; Enl.Ht.; I or IIA; N.R.
48.7			4650	123.6	667	Unk.; M.S. and M.I.; A.I.; I; N.R.
34.2			3940	135.7	764	Unk.; M.S. and M.I.; A.I.; I; N.R.
52.8			4350	141.1	809	Rh.; M.S. and M.I.; A.I.; Enl.Ht.; I; N.R.
66.5	13.0	8.3	3900	149.1	879	Rh.; M.S. and M.I.; A.I.; sl.E.H.; I; N.R.
94.6	12.8	8.2	4700	127.1	691	Rh.; R-I-V-HB; M.S. and M.I.; A.I.; marked E.H.; IIA; N.R.
33.5			2970	124.1	668	Rh.; M.S. and M.I.; A.S. and A.I.; ? E.H.; IIA; N.R.
21.0	10.7	8.2	2850	106.9	551	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; I; N.R.
57.3			4300	180.0	1178	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
46.7			4230	180.0‡	1178‡	
44.4			4210	180.0‡	1178‡	
40.0	19.5		3100	119.2	629	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; IIA; N.R.
27.0	16.6	6.8	2800	121.6	647	Unk.; M.I., M.S., A.I., and A.S.; Enl.Ht.; I; N.R.
55.9	16.4	7.6	4000	113.0	580	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; I; N.R.
34.8			3100	247.6	1882	Rh.; M.S. and M.I.; A.S. and A.I.; marked E.H.; IIA; N.R.
49.7	22.9	7.3	2500	170.8	1080	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
61.7			3625	164.2	1015	Rh.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
43.9			3700	168.6	1055	Unk.; M.S. and M.I.; A.S. and A.I.; Enl.Ht.; IIA; N.R.
34.4	25.0	10.2	2450	151.5	899	Rh.; M.I., M.S., A.I., and A.S.; Enl.Ht.; IIA; N.R.
52.0	15.6	6.7	2600	125.8	678	

There was no significant difference in any of the measurements in the four etiological groups during heart failure (figures 1 *a, b, c*).

Observations Made after Recovery from Heart Failure

There are 31 observations on 23 subjects. The average cardiac index was decreased to 1.73 liters (normal 2.09 liters), the average decrease being greater in the rheumatic group than in the miscellaneous group (tables 2 and 3; figures 2 *a, b, c*).

The average arteriovenous oxygen difference was increased to 76.9 c.c. (normal 61.5 c.c.), the average stroke volume decreased to 44 c.c. (normal, 59 c.c.); the average venous pressure was 7.3 cm. (normal range), and the circulation time was prolonged to 23.7 sec. (normal, 14.4 sec.). There were no marked differences in the etiological groups.

Observations Made before the Occurrence of Heart Failure

There are 46 observations on 39 patients. The average cardiac index was reduced to 1.87 liters (normal, 2.09 liters; tables 2 and 4; figures 2 *a, b, c*), the average arteriovenous oxygen difference increased to 71.4 c.c. (normal, 61.5 c.c.), the stroke volume decreased to 43 c.c. (normal, 59 c.c.), the average venous pressure was 8.1 cm. (normal range), and the circulation time 15.4 sec. (normal range).

Discussion

These data show that in the presence of congestive heart failure there is marked decrease in the functional capacity of the heart in that it pumps less blood per square meter of body surface per minute than does a normal heart, that the output per beat is decreased, that the blood consequently circulates at a reduced velocity, shown by the prolongation of the circulation time, and that there is usually rise in venous pressure. The arteriovenous oxygen difference is increased.

Patients who have organic heart disease but have not suffered failure show, on the average, a slight decrease in cardiac index and output per beat, increase in arteriovenous oxygen difference but no significant change in circulation time and venous pressure.

On the other hand, patients who have recovered from congestive heart failure show values intermediate between those exhibiting failure and those who have never experienced failure; that is to say, the cardiac index is greater than during failure but not as near normal levels as before heart failure occurred. The circulation time is prolonged but shorter than during failure.

It appears, therefore, that during failure the heart is less effective as a pump than it is in a normal individual and less effective than a heart that is damaged by organic heart disease but has not been subjected to failure, and

also less effective than is an organically diseased heart after it has recovered compensation.

These changes are not associated with alterations in basal metabolic rate. The average progression appears to be slight decrease in cardiac output per beat and per minute in patients exhibiting organic heart disease before the occurrence of failure, a greater decrease in those recovered from failure, and a still greater decrease in the presence of congestive heart failure. This trend is illustrated further in the case of those patients studied both during failure and after return to compensation (tables 1 and 3; figure 3), since in them cardiac output per minute and per beat is less during failure than after compensation has been restored. These results are in agreement with those recorded by Stewart and Cohn,[1] Stewart, Deitrick, Crane, and Wheeler [3] and Stewart, Deitrick, Watson, Wheeler, and Crane.[14] The observations of McGuire, Shore, Hauenstein, and Goldman [15, 16] point to similar conclusions. Harrison, Friedman, Clark, and Resnik,[17] however, were of the opinion that "the level of the cardiac output per minute, whether considered as such or in relation to the metabolic rate, bears no relation to the presence or absence of congestive failure." McGuire [15] has analyzed the discrepancy between Harrison's results and his, and we have already discussed differences between Harrison's results and ours.[3] Our observations confirm the notion expressed in our earlier papers [1, 3, 14] and lend support to the opinion arrived at by Altschule [18] in his excellent analysis of the data which were available at that time, namely that "the fundamental defect (in congestive heart failure *), however, is a cardiac output which, in relation to the metabolic requirements of the body and to the venous return, is abnormally lowered."

The heart size was larger during failure than after recovery from failure in those in whom the comparison was possible (tables 1 and 3), a finding to which Stewart and Cohn [1] and Stewart, Deitrick, Crane and Wheeler [3] have already directed attention. The work of the left ventricle per beat in its relation to heart size has been studied with respect to the functional state of the patients (tables 1, 3 and 4; figure 4). Stewart and Cohn [1] expressed the opinion that the explanation of increase in cardiac output with decrease in cardiac size as a consequence of giving digitalis was to be found in Starling's [19] "law of the heart." Starr and his associates [11, 20] have presented data since then showing that this "law" applies to basal cardiac work in human beings as well as to that in heart-lung preparations, since they found that the work of the left ventricle which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data, they defined a zone of normal circulatory function. In a manner similar to theirs, we have plotted cardiac volumes as abscissae and grammeters of work of the left ventricle per beat as ordinates (tables 1, 3 and 4; figure 4). During heart failure (figure 3 *d* and *e*), the values for all except two patients

* Parenthetical statement introduced by H. J. S. to carry over the context of the preceding sentence.

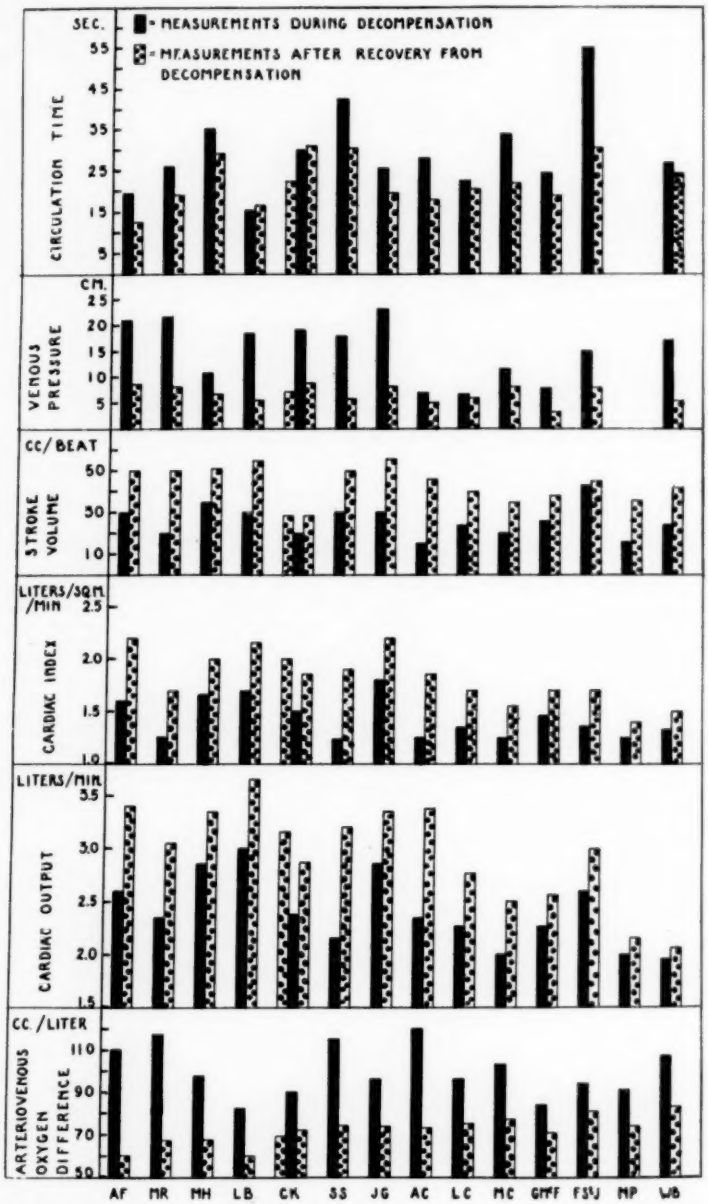

FIG. 3. In this figure are plotted data from tables 1 and 3 relating to patients studied during cardiac decompensation and again after recovery from failure.

fell outside and below line CD, in an area, indicating that in them the work of the heart was not commensurate with size. In those recovered from failure (figure 4 *c* and *e*), a greater number were inside the normal zone, and others have moved closer to line CD; in short, they were not so far outside the normal zone. On the other hand, in those patients suffering from heart

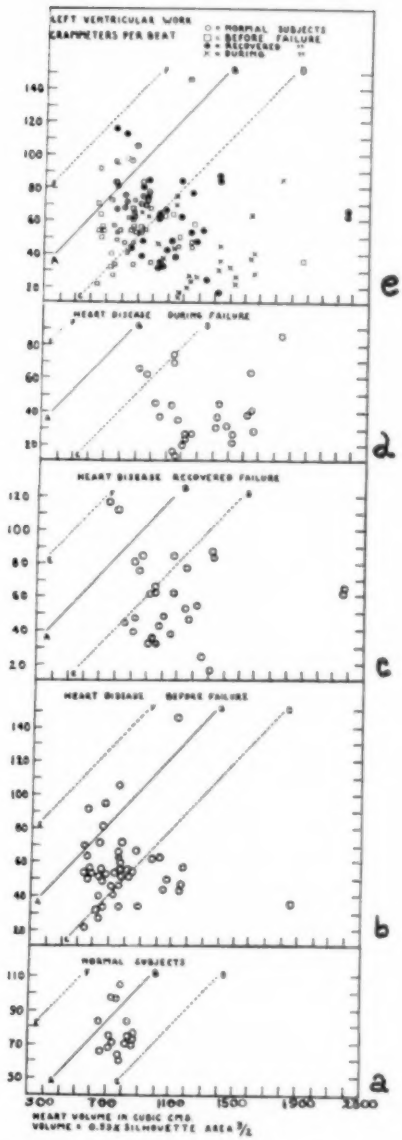

FIG. 4. Left ventricular work per beat and cardiac volume. The data from tables 1, 3 and 4 relating to work of the left ventricle per beat in patients suffering from heart disease are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on area, defined by Starr, Collins, and Wood on the basis of a statistical treatment of data from a control group of cases. Lines *CD* and *EF* are placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient falling within zone *CD–EF* has a normal circulatory function; that is to say, the work of the heart is commensurate with its size. On the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. Each symbol represents a measurement in the group as indicated. In figure 4*b* are data relating to measurements made of cardiac patients before the occurrence of failure; in figure 4*c*, data in those recovered from failure; and in figure 4*d* data collected during heart failure. In figure 4*a* are given normal data for comparison. In figure 4*e*, the data from figure 4, *a*, *b*, *c*, *d* are plotted on one chart for comparison.

disease who had never experienced failure, most fall in the normal zone, and a few who fall below line CD take a closer position on the whole than those in failure and those recovered from failure (figure 4 *b* and *c*). In those studied in both states, failure and compensation, arrows indicate their improved position on the chart with return to compensation (figure 5).

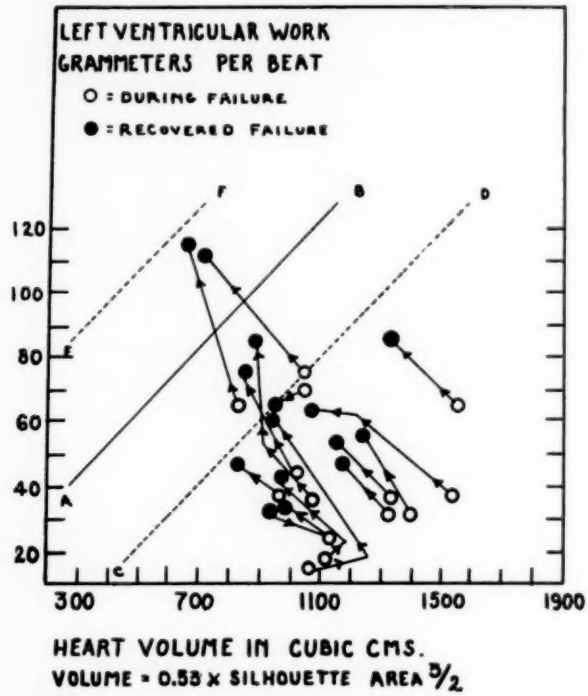

FIG. 5. Left ventricular work per beat and cardiac volume. The data of tables 1 and 3 relating to work of the left ventricle per beat are plotted against cardiac volume in those patients in figure 3 in whom observations were made during failure and again after recovery, in a manner similar to figure 4. Arrows indicate the shift in position on the diagram with return to compensation.

The spread of data in the frequency charts (figure 2 *a, b, c*) shows overlapping of values in the different clinical functional states. This is not unexpected, since not only the extent of valvular and myocardial damage differs from patient to patient, but also individual variations in the adjustments of the circulatory apparatus and of the organism as a whole are to be expected.

In the light of our observations, heart failure does not appear to fall into the categories of " right-sided " or the " left-sided " variety, nor do the concepts of " backward " failure or " forward " failure appear to us to explain heart failure as it is most frequently encountered in the clinic. The general use of these terms when applied to heart failure gives rise to sureness which the facts do not warrant, and from these labels arises a security which acts as a deterrent to further progress in the understanding of the mechanism of heart failure.

Summary

Certain circulatory measurements have been made of patients exhibiting organic heart disease of the four common etiological types, namely rheumatic, arteriosclerotic, hypertensive, and syphilitic. It appears that:

(1) Organic heart disease in patients who have not experienced failure is associated with decrease in cardiac index and in cardiac output per beat.

(2) The cardiac output per minute and cardiac output per beat are decreased further in the presence of congestive heart failure.

(3) As compensation is restored, there is increase in cardiac index and in cardiac output per beat. The values do not usually, however, achieve the level prevailing before the occurrence of failure; they take a position intermediate between those made during failure and those made in patients who have never experienced failure.

(4) The venous pressure is usually elevated in congestive heart failure.

(5) The average circulation time is prolonged in patients suffering from congestive heart failure and in those recovered from failure, but the average value is normal in those who have not experienced failure.

(6) The arteriovenous oxygen difference is increased slightly in organic heart disease, more after recovery from failure, and still more in the presence of heart failure.

(7) The work of the heart per beat in relation to its size may be normal or show slight decrease in the presence of heart disease before failure occurs. In the presence of heart failure, there is a marked discrepancy between the size of the heart and the work, so that the values fall outside the zone of normal circulatory function. After recovery, the heart size-work relationship is restored toward the normal level so that the position on the chart moves closer to or into the normal zone.

Conclusions

There is marked decrease in the functional capacity of the heart as a pump in congestive heart failure as shown by the decrease in cardiac output per minute per square meter of body surface (cardiac index) and per beat; prolongation of the circulation time occurs, as also may rise in venous pressure. Moreover, the size of the heart increases. Since the output per beat is decreased, and the heart size is larger, the work per beat is no longer commensurate with the size of the heart. With restoration of compensation the functional capacity is increased toward a normal level but on the average does not attain the level of which it was capable before the onset of failure.

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CASE REPORTS

HEMOCHROMATOSIS: REPORT OF A CASE IN WHICH TUBERCULOUS PERITONITIS WAS A COMPLICATION *

By Carl G. Morlock, M.D., F.A.C.P., *Rochester, Minnesota*

Hemochromatosis is a disease of infrequent occurrence. Sheldon, in 1935, accepted a total of 311 reported cases as genuine. Butt and Wilder have added 30 cases which were observed at The Mayo Clinic in 15 years. Stewart emphasized the rarity of the disease by showing that its incidence was 0.136 per cent in the necropsies performed in the British hospitals. Althausen and Kerr determined that the incidence of the disease varied from 0.003 per cent among 106,000 patients who were admitted to Johns Hopkins Hospital to 0.005 per cent among 60,000 patients who were admitted to the University of California Hospital. The disease has a remarkable age incidence: in most cases the patients are between 45 and 55 years of age. There is an unusual predominance of the disease among men. Sheldon found only 13 authentic instances of the disease among females, and in the series of cases reported by Butt and Wilder only one patient was a female.

There are many other remarkable features of this disease which have induced Sheldon to name it a " key disease " and to make a plea for a most intimate study of the condition. It is because of these facts and the unusual features in a case observed at the clinic that I have been prompted to consider it worthy of record.

Case Report

A white man, aged 54, sought advice at the clinic because of abdominal pain and ascites. He had been in excellent health all of his life except for the usual diseases of childhood and an elevated blood pressure, which had been discovered a year before he came to the clinic. He was an electrical engineer and had never been exposed to poisoning by any of the heavy metals. On close inquiry his wife volunteered that eight years before the patient came to the clinic she had noted a darkening of the skin of his face and hands, which she had attributed to excessive exposure to sunlight. Three months before his admission he had had a sore throat, high fever and delirium. During a slow convalescence he had suffered from dull, persistent pain in the lower part of the abdomen. Loss of strength had become pronounced and cardiac and respiratory embarrassment had developed as a result of progressively increasing abdominal distention.

When the patient was examined at the clinic he obviously was ill. His temperature was 100° F., the pulse rate was rapid, and there was evidence of orthopnea. The abdomen was tender and filled with fluid. The edge of the liver was palpable 4.5 cm. below the costal margin. The most striking feature was the dusky, cyanotic, grayish-brown color of the face. The skin was dry; there was a definite brown metallic pigmentation of the hands, forearms and legs; this was visible to a lesser extent on the remainder of the body. The palmar creases were sharply defined by a brownish melanin-like pigmentation. The buccal mucosa was free of pigment, but

* Received for publication November 14, 1938.

it and the tongue were smooth and cherry red in color. The pigmentation resembled most closely that of Addison's disease, although it was not entirely characteristic of this condition. There was in addition a slight scleral icterus. The genitalia were atrophic; the prostate gland was soft and small.

The patient was admitted to the hospital for observation. He had an intermittent fever which reached a peak of 104° F. A salt-free, low-protein, high-carbohydrate diet, the oral administration of ammonium nitrate, the intravenous administration of a concentrated solution of d-glucose and salyrgan did not enable the patient to maintain a favorable water balance. The abdominal distention increased in amount. A diagnostic and therapeutic abdominal paracentesis was performed and 7000 c.c. of straw-colored fluid were removed. The fluid contained a few erythrocytes and leukocytes; the concentration of total protein was 3.74 gm. per 100 c.c. A special search did not reveal any acid-fast bacilli or malignant cells in this fluid. The high concentration of protein in the ascitic fluid indicated that it was not a simple transudate but an accumulation of fluid caused by an intraabdominal inflammatory process.

The urine was normal except for a slight reduction of Benedict's reagent by several specimens. The flocculation test for syphilis was negative. The concentration of hemoglobin was 14.6 gm. per 100 c.c. of blood; the erythrocyte count and the leukocyte count were 4,220,000 and 10,700, respectively, per cubic millimeter of blood. The differential blood count disclosed 91 per cent neutrophiles and a definite macrocytosis. The concentration of urea varied between 22 and 46 mg. per 100 c.c. of blood. On three different occasions the values for the fasting blood sugar were reported as 113, 120 and 91 mg. per 100 c.c. The concentration of serum bilirubin was 2.8 mg. per 100 c.c. and the Van den Bergh reaction was direct. A bromsulphthalein function test disclosed retention, grade 3. The concentration of plasma chloride was 562 mg. per 100 c.c.; the concentration of serum sodium was 296 mg. per 100 c.c.; the concentration of serum potassium was 19.7 mg. per 100 c.c.; the concentration of plasma cholesterol was 88 mg. per 100 c.c.; the concentration of plasma cholesterol esters was 44 mg. per 100 c.c.; the concentration of plasma lecithin was 147 mg. per 100 c.c., and the concentration of plasma lipoids was 255 mg. per 100 c.c. The value for serum protein was 7.9 gm. per 100 c.c. and the albumin-globulin ratio was 1 : 1.7. The colloidal osmotic pressure of the blood was 293 mm. of water. The sedimentation rate of the erythrocytes was 86 mm. at the end of one hour. Spectroscopic examination of the blood did not disclose any abnormality. Cultures of the blood on blood agar and brain broth did not produce any growth in 48 hours. A roentgenogram of the thorax revealed old healed tuberculous lesions in the apices of both lungs.

On the basis of the pigmentation of the skin, the demonstrable injury of the liver, the borderline level of the concentration of blood sugar, and the macrocytosis, a diagnosis of hemochromatosis with cirrhosis of the liver was made. The cause of the peritoneal exudate was not evident. The patient did not respond to therapeutic measures but his condition became rapidly worse than it had been. Bronchopneumonia and thrombosis of the right femoral vein developed and the patient died.

Necropsy disclosed that the peritoneal cavity contained 800 c.c. of yellow purulent fluid. There were many adhesions and the parietal and visceral portions of the peritoneum were covered with a reddened granular exudate and were studded with multiple discrete and confluent nodules. Microscopic examination disclosed that these nodules were tubercles. Healed tuberculosis was found in the apices of both lungs; the hilus nodes were involved in an active caseating tuberculous process. The heart weighed 403 gm.; the spleen weighed 370 gm. (normal weight 200 gm.), and the liver weighed 2648 gm. (normal weight 2000 gm.). The liver was a dark bronze color; its surface was nodular and hobnail in type; the cut surface was firm and colored brown. In addition to that of the skin and liver, there was macroscopic evidence of pigmentation of the pancreas, heart, adrenal glands, thyroid gland, prostate gland and seminal vesicles.

Microscopic examination disclosed a diffuse tuberculous peritonitis that involved the entire parietal and visceral peritoneum. Most marked of all the microscopic findings was the pigmentation which was readily demonstrated to be the result of an iron-containing compound. The pigment was present in great quantity in the liver (figure 1*a*) where it had permeated the extracellular fibrous tissue and was found in lesser

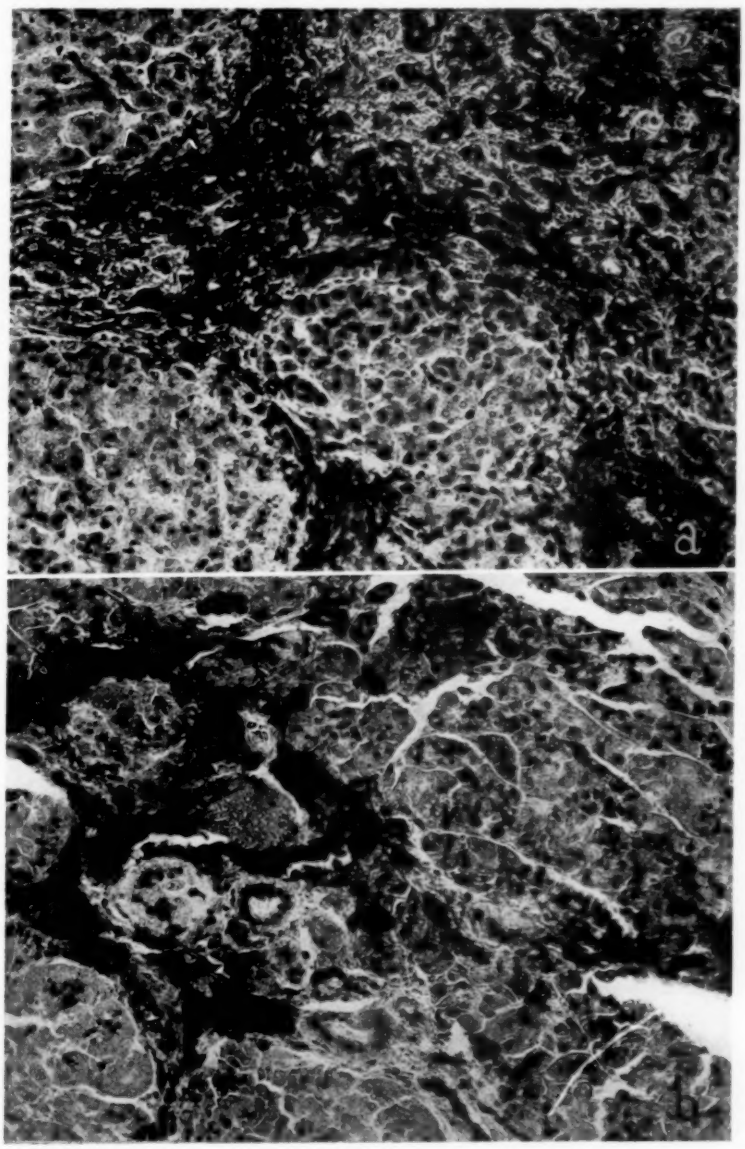

FIG. 1*a*. Section of liver showing marked cirrhosis; hemosiderin granules are clearly evident in the fibrous tissue stroma but less so in the parenchymal cells; section stained with potassium ferrocyanide and basic fuchsin (× 145); *b*, section of pancreas showing increase in fibrous tissue and heavy deposits of hemosiderin in the fibrous tissue and in the parenchymal cells; specimen stained with potassium ferrocyanide and basic fuchsin (× 145).

degree in the parenchymal cells. There was a considerable increase of fibrous tissue in the liver and a well-marked cirrhosis. Pigment was extensively deposited in the pancreas (figure 1*b*), where an increase of fibrous tissue was marked. It is at once evident that although the most extensive deposit of pigment occurred in the extracellular fibrous tissue, much pigment also was deposited in the parenchymal cells both of the islets of Langerhans and the glands of external secretion. In the spleen, iron-containing pigment was present in the pulp cells and fibrous tissue of the trabeculae. Considerable iron-containing pigment also was evident in the mucosal cells of the stomach, in the myocardium (figure 2), in the glandular epithelium of the thyroid,

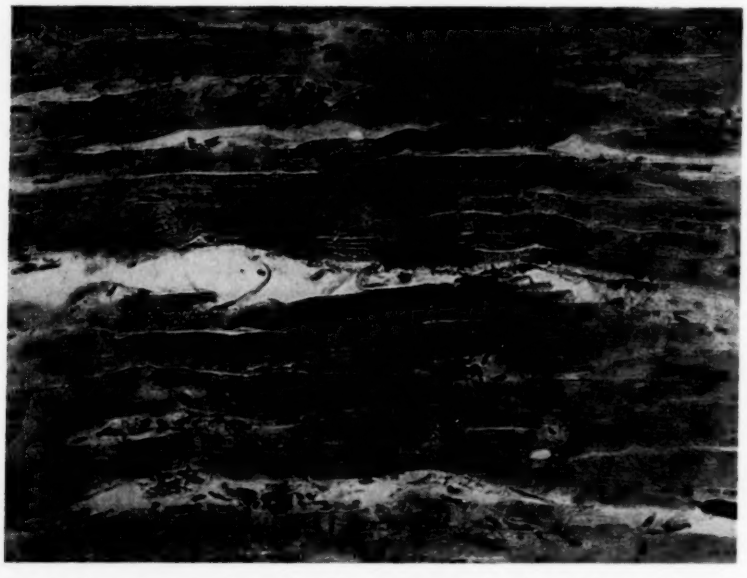

FIG. 2. Section of myocardium showing extensive deposit of dark staining hemosiderin granules in the muscle fibers; section stained with potassium ferrocyanide and basic fuchsin (× 200).

adrenal and prostate glands, and in the interstitial cells of the testes. In the skin, iron-containing pigment was evident in minor degree in the sudoriferous glands. It has been stated that the kidney escapes pigmentation, but in this case pigment was found in isolated portions of the tubular epithelium and to a lesser extent in the glomerular epithelium.

COMMENT

General Features of the Disease. The first symptoms of this disease, which occur with equal frequency, are diabetes, some abdominal symptom such as pain or visceral enlargement, and pigmentation of the skin. In this case pigmentation of the skin occurred first. Pigmentation occurs in 80 per cent of cases; it usually is bronze or a bluish metallic color which resembles the color of slate. The whole body is usually affected, but it is characteristic that the face, the extensor surfaces of the forearms and the dorsa of the hands are most involved. One striking observation was the occurrence of pigmentation of the buccal mucosa in 16 per cent of cases.

That diabetes is sometimes a late sequela of the disease is suggested by this

case, for although a slight glycosuria was noted in occasional specimens of urine the values for the fasting blood sugar were within the normal range. When diabetes is once established in these cases it often becomes rapidly severe and extremely difficult to control. Sometimes the diabetes is refractory to the use of insulin.

Hepatomegaly and ascites are the most commonly encountered abdominal symptoms. Sheldon found reference to jaundice in only seven cases. In the case that I am reporting there was a definite, though minimal, clinical jaundice and elevation of the concentration of serum bilirubin.

Sexual hypoplasia that is associated with genital atrophy, loss of hair and impotence has been noted. It has been postulated that this is secondary to the glandular dysfunction caused by deposit of pigment in the pituitary body.

Sheldon said that the average duration of the disease is 18.5 months after the first symptom becomes obvious enough to induce the patient to seek medical advice. In the case that I am reporting abnormality of pigmentation had been noted, but had not been considered significant, at least eight years before death.

Tuberculosis was the precipitating cause of death in this case and has been the cause of death in 9 per cent of all cases of hemochromatosis. Diabetes and its complications account for more than half the deaths in cases of this disease.

Pigmentation. There are two demonstrable pigments concerned in hemochromatosis. One is hemosiderin, an iron-containing compound, which is believed to be a ferric hydrate of colloidal nature that is loosely bound with fat and protein. This pigment occurs in the secreting cells of the glands of both internal and external secretion; in the connective tissue of these organs; in the lymph nodes; in striated muscle, especially that of the heart; in the reticuloendothelial system; in the alveolar epithelium of the lungs; in the cartilages and synovia of joints; and occasionally in the walls of blood vessels.

The second pigment, hemofuscin, is found in the epithelial cells of glandular organs; extracellularly in the connective tissue of these organs; in smooth muscle; and most extensively in the walls of the medium-sized and small arteries. Hemofuscin is a pigment which has been described as dark brown, black or yellowish-brown. It does not react to any of the microchemical tests for iron and actually does not contain iron. It is readily stained by the basic aniline dyes and is believed to be related to the melanins.

Theories of Etiology of the Disease. Many theories have been advanced to explain the production of this disease. Some men believe that it is due to the destruction of blood and the accumulation of pigment left by the normal wear and tear of the erythrocytes. Diabetes mellitus and cirrhosis of the liver have been cited as primary disturbances responsible for the disease. Toxic factors have been suggested, and in turn bacteriologic toxins, alcohol, zinc, lead, and copper have been eliminated as causative agents.

The idea that the fundamental nature of the disease consists of a disorder of metabolism has much to commend it. The theory which has met the widest acceptance is that the tissues have an abnormal avidity for iron. In general, however, even this explanation is unsatisfactory, its most obvious failing being that it concerns only an explanation for the deposits of hemosiderin; it does not consider the simultaneous deposit of hemofuscin.

The most feasible suggestion for the accumulation of hemosiderin is that there is some abnormality in the removal of iron from the cell in the normal

cycle of entrance and exit; thus there is piled up a useless residuum of iron which eventually bursts and kills the cell which contains it. As a result, the iron is found in an extracellular situation after death. One difficulty in proving this theory is the limitation which clinical methods impose in the evaluation of the metabolism of iron. Dry, as a result of a very carefully balanced experiment, concluded that in cases of hemochromatosis there is not an increased retention of iron as compared to normal. However, it may be argued that the average daily retention needed to accumulate the large amounts of iron in the tissues, is too small to be appreciated by this type of experiment unless it is very prolonged. This theory of the deposit of iron-containing pigment has the disadvantage that striated muscle is relatively unaffected; however, the theory is supported by the fact that as age advances the accumulation of pigment becomes more pronounced and that in really rapidly growing cells, such as cancer cells, there is scant deposition of the pigment.

The deposits of hemofuscin appear to be a part of a disturbance of the metabolism of melanin, which equally with that of iron must be regarded as one of the essential features of hemochromatosis. That one is justified in considering an alteration in the metabolism of melanin as one of the characteristic features of the disease is indicated by the fact that one of the main clinical features, namely pigmentation of the skin, is in all cases largely, and in some cases solely, due to a great increase in the melanin content of the deeper layers of the epidermis. Especially noteworthy is the fact that hemochromatosis has been complicated by melanuria.

The most reasonable explanation of hemochromatosis is that it is due to an inborn error of metabolism which is far more common among males and which at times actually has a familial incidence.[4] The error concerns the inner metabolism of probably all the cells of the body. The production of pigment may be the result of a disturbance of the normal changes in intracellular chemistry which are dependent on the processes of aging of the cell. The hypothesis of an error of metabolism appears to be the only one which will encompass the enormous array of facts provided by the clinical, pathologic and chemical aspects of the disease.

Comment

The absence of significant clinical diabetes and the presence of jaundice in this case are noteworthy. The pigmentation of the exposed surfaces of the body and of the palmar creases suggested an Addisonian pigmentation rather than hemochromatosis.

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CHRONIC LEUKOPENIA WITH FATAL TERMINATION DUE TO AGRANULOCYTIC ANGINA; CASE REPORT *

By Israel Kopp, M.D., *Boston, Massachusetts*

The literature now contains many case reports of agranulocytosis since its first description by Schultz in 1922.[1] Various hypotheses as to its etiology have been offered, and a number of drugs, nearly all containing the benzene ring, have been implicated.[2, 3, 4]

Agranulocytosis has been defined as a disease in which essentially there is a marked diminution or total absence of the granulocytes of the peripheral blood, which is followed by a loss of cellular resistance as shown by infectious processes of various types.[4] Various other descriptive terms have been given to this syndrome, such as agranulocytic angina, primary granulocytopenia and idiopathic or primary or malignant neutropenia. The term pernicious leukopenia was proposed by Fitz-Hugh [2] in place of those mentioned above to indicate that all the leukocytes were diminished, whereas all other terms emphasized only the most striking feature of the disease, i.e., a marked reduction in the granulocytes.

Cases of recurrent and chronic granulocytopenia or neutropenia have been reported by numerous observers.[5, 6, 7, 8, 9, 10, 11] In the recurrent form the disease is cyclic, acute exacerbations occurring at variable intervals with or without relationship to other factors such as the menstrual flow, drug ingestion, vaccines, etc. The white cell count between recurrences is in some cases within normal limits, with polymorphonuclear neutrophiles quantitatively and qualitatively normal, and in other cases reveals for a prolonged period granulocytopenia.

In the chronic form of granulocytopenia the white cell count remains low and ranges from 2500 to 5000.[12] The cells are normal in appearance and percentage relationship. In some patients this low white cell count is accompanied by good health and a normal response to infection. In others, vague symptoms are present and the polymorphonuclear neutrophile response to demands above that normally made on the body (such as an infection) is inadequate.

We wish to report a case of marked leukopenia of at least four and a half years' duration and of unknown etiology, which terminated fatally in agranulocytic angina. Of considerable interest in this patient is the transition of a marked leukopenia with all the white cell elements absolutely, but not relatively, diminished to one of a typical agranulocytic angina.

Case Report

The patient, D. F., aged 49 years, a married male, a building contractor by occupation, was seen on February 6, 1934, with dizziness the chief complaint. For the past few years he had experienced dizziness, which had been relieved at first by the wearing of glasses, but which of late had become worse. He experienced occasional generalized headaches which resembled those "after a night's drinking" and were relieved somewhat by squeezing the frontal area. He complained also of occasional buzzing and whistling in the ears and insomnia. His memory had become poor. There was some dyspnea on going up an incline, due probably to his obesity. There were shooting rheumatic pains in the left lower extremity and occasional pains in the left knee-joint relieved by exercising the joint.

* Received for publication February 1, 1939.
From the Boston Psychopathic Hospital.

The patient was an Italian by birth and accustomed to taking about one quart of wine daily.

The past history revealed gonorrhea at the age of 25 with adequate treatment.

Physical examination revealed a tall (71 inches), well nourished, obese patient (weight 225 pounds), with a large protuberant abdomen. Other significant findings were as follows:

The pupils were equal, the right slightly irregular; the reactions to light and accommodation were normal. The tonsils were small, adherent and moderately injected. The heart and lungs were negative. Blood pressure was 145 mm. of mercury systolic and 95 diastolic. Neurological examination was negative except for equally diminished patellar reflexes. The Wassermann reaction of the blood was negative. Urine examination was negative. Lumbar puncture was advised but refused. Results of blood examinations done when the patient was first seen and on subsequent visits are shown in table 1.

Since the patient was quite concerned about his insomnia, 3 grains of sodium amytal were prescribed. This medication was taken on two occasions only. Close questioning revealed that two months before (December 1933) another physician had prescribed a tablet medication of which he took three a day for two weeks. Occasionally the patient had taken potassium iodide, 40 drops daily, as a medication for rheumatism.

From February 6, 1934 to May 12, 1934 the blood was examined on six occasions and on each revealed a marked leukopenia, the various white cell elements being absolutely but not relatively diminished (table 1). The patient's chief complaints during this period were dizziness and insomnia. He was not seen again until January 1938. He had enjoyed very good health in the interim and had gained weight. His chief complaint at this time was abdominal discomfort especially after meals. The hearing of the right ear was impaired and insomnia was still present. He had continued to take one quart of wine daily. The physical examination revealed nothing new. In view of the obesity and the difficulty in palpating the abdomen a roentgen-ray of the abdomen was taken and revealed the following:

"The liver is not well outlined but is probably normal. There is a suggestion of a large mass in the left side of the abdomen which might well be an enlarged spleen and seems definitely too large for kidney."

A roentgen-ray of the chest revealed no pathologic process. Pentnucleotide therapy was advised but was refused by the patient.

The patient was again seen on August 3, 1938. There were no complaints except for some pain in the left knee-joint. He was in good physical condition and had gained 25 pounds in weight. A roentgen-ray of both knee-joints revealed some arthritic changes. A roentgen-ray of the abdomen was interpreted as follows:

"The shadow in the left abdomen thought to be an enlarged spleen is only suggested today and seems rather more like kidney than spleen. Not so large as previously."

A blood examination revealed again a marked leukopenia with 45 per cent polymorphonuclear neutrophiles (table 1).

On August 28, 1938 the patient was admitted to the Beth Israel Hospital in a critical condition.* For the preceding three weeks he had suffered from severe headaches and soreness of the mouth. Roentgen-rays of the teeth had revealed two "infected teeth" which were removed two weeks before entry. Since that time he had taken numerous tablets of anacin † and lullit † and had in one day ingested a total

* We wish to thank Drs. Harry Linenthal and William Dameshek for permission to use the clinical and laboratory data, and Dr. Bernard Goldberg for many helpful suggestions and criticisms.

† Both anacin and lullit contain acetphenetidin, acetylsalicylic acid and caffein.

TABLE I

Date	Hb. (Sahli) 13.8 gm. = 100%	Red Count	White Count	Per Cent								
				Neutrophiles	Basophiles	Eosinophiles	Myelocytes	Myeloblasts	Metamyelocytes	Large Lymphocytes	Small Lymphocytes	Monocytes
2- 6-34	90	5,470,000	1000* 1500 2200	52	1	3				15	27	2
2- 8-34	85	5,705,000	1250* 2250	43	4	4				9	39	1
2-28-34	95	6,330,000	2550	53	4	1	1			5	33	3
3-15-34	97	5,955,000	2200* 2650	60	3	2				12	18	5
4-22-34	85**	5,500,000	2600	62	1	2			1	9	20	5
5-12-34	85**	6,100,000	1875	58	2	4			2	10	21	3
1-25-38	85	5,610,000	875	46	2	4	2	2		7	37	
8- 3-38	86	4,385,000	800* 1200	45	3			1	1	13	36	1

* Different pipettes.
** Tallqvist.

of 35 grains of acetphenetidin. Mouth washes had also been prescribed. The headaches became worse, the mouth more sore. About one week before entry "pus" formed about his gums. At this time, because of the severe headaches and progressive weakness, the patient went to bed. Six days before entry, twitchings of the hands and legs were constantly present. Three days before entry he told his family that something "had burst inside of his head," following which the headache disappeared entirely.

Physical examination revealed a well developed and obese male, mildly confused. Both ear-drums were markedly injected. The conjunctivae were injected and there was a slight icteric tint to the sclerae. The gums were soft, red and spongy. Pressure at the gum margins caused exudations of pus. The tongue was heavily coated. A thick, white, tenacious membrane covered the hard palate and portions of the gums. The pharynx was moderately injected. There was a mild cervical adenopathy. The lungs revealed dullness and diminished breathing, tactile and vocal fremitus at the right base. Over the latter area and in both axillae many medium moist râles were heard. The heart was negative. The pulse was 120, the temperature 104° F., and the blood pressure 140 systolic and 78 diastolic. Blood examinations and other laboratory data are shown in chart 2. On August 29 the patient was quite toxic, and the mouth showed many ulcerations and a foul purulent discharge.

Treatment consisted of adenosine sulphate, 2 grams in 125 c.c. of saline, on the night of admission, and on the following day 1.4 grams in 150 c.c. of saline, a transfusion of 500 c.c. of blood, and an intravenous infusion of 1000 c.c. of saline and glucose 2½ per cent.

The dullness at both bases increased with the appearance of moist bubbling râles. The patient's condition became worse; the temperature remained elevated, ranging from 104 to 105.5° F.; the pulse rate fluctuated from 90 to 125; and the respirations rose from 30 to 50. He became incontinent of both urine and feces, semicomatose, and died on August 31. Permission for a postmortem examination was not obtained.

Discussion

The patient presented a marked leukopenia on each blood examination during 1934 and 1938. The various white cell elements were quantitatively but not qualitatively or relatively affected. Jackson and Parker [3] state that the majority of patients with leukopenia have some well recognized fundamental disorder to account for this, and that in some instances the leukopenia is unrelated primarily to the hematopoietic system. No etiology could be found for the leukopenia, and though this was at times fairly marked the patient enjoyed very good health for four and a half years. One can only conjecture as to the white cell count from 1934 to 1938. At no time was there any evidence of a significant lymphadenopathy. Splenomegaly was not found on repeated physical examinations, and the roentgen-ray conclusions in regard to this were inconclusive.

Individuals may exhibit a chronic leukopenia with few and vague symptoms.[12] The white cells may remain well below 4000 or show periodic fluctuations varying from normal to a severe leukopenia. In some, white cell counts of 2500 to 5000 occur with no symptoms, and the response to any infection is prompt and adequate, both quantitatively and qualitatively. In others, demands over and above that physiologically required cause a more severe leukopenia and not a leukocytosis. The bone marrow, with its low reserve of myelocytes, cannot respond, and a minor infection may lower still further the patient's resistance.[12] The white cell count of our patient was usually lower than 2000 cells, and probably belongs to the latter group of patients with chronic leukopenia.

TABLE II

Date	Hb. (Sahli)	Red Count	White Count	Smear	Other Data
8–28–38	80	3,490,000	350	24 cells counted. Polynuclear neutrophiles 3. Lymphocytes 16. Polymorphonuclear leukocytes toxic with variation in size and shape and staining of granules. Lymphocytes vacuolated and atypical. No small lymphocytes seen. Metamyelocytes 2. Unclassified 3	
8–29–38	* 74 (11.5 gm.)	3,670,000	1350 a.m. 700 p.m.	11 cells seen: 1 polynuclear neutrophile and 10 lymphocytes	Platelets 264,240. Reticulocytes 0.5%. CO_2 combining power 56.7%. Stool examination negative. N.P.N. 42 mg. Icteric index 10. Blood sugar 221 mg. Calcium 8.6 mg.
8–30–38	76	4,380,000	700 a.m. 500 p.m. 300 p.m.		Throat culture negative for hemolytic streptococci. Urine examinations show v.s.t. of albumin, 6–8 white cells per high power field and 2–4 fine granular casts

* Evelyn Colorimeter.

In view of the persistent and marked leukopenia other blood disturbances must be considered. The absence of splenomegaly, of gastrointestinal bleeding, and of an anemia (except for the anemia prior to death) over a period of four and a half years are against Banti's disease. Though platelet counts were not done prior to the fatal illness they did not appear diminished from the examination of the blood smears. The patient's age and the absence of symptoms and physical findings, of abnormal or disproportionate increase in abnormal lymphocyte cells, and of an anemia rule against a diagnosis of aleukemic leukemia. The absence of anemia and bleeding, of a history of exposure to roentgen-ray or radium or the administration of benzol or arsenic derivatives eliminates the possibility of an aplastic anemia.

The patient himself had been questioned as to any drug ingestion at the time of each blood examination, and as far as can be determined had taken aspirin tablets only for his headaches and pains in the left knee. He had been advised by friends to take potassium iodide for his arthritis. The amytal medication, which had been prescribed after the first blood examination had revealed a leukopenia, did not affect the blood picture, since it has been shown that the barbituric acid derivatives do not produce agranulocytic angina.[2] If the history as obtained from the relatives can be considered accurate the symptoms of his fatal illness had already started even before any drugs containing acetphenetidin had been taken. Of more than 379 cases of agranulocytic angina reported up to the year 1938, Kracke [13] noted only three as possibly related to the ingestion of acetphenetidin and concluded that the evidence is not as yet adequate that phenacetin is capable of producing agranulocytosis.

It is of interest that the white cell count in January 1938 was 875, with 46 per cent neutrophiles, and on August 3, 1938, a few days prior to the onset of his final illness, 800 and 1200, with 45 per cent neutrophiles. The red cell count obtained at the later date showed a distinct drop from that of January, a fall from 5,610,000 to 4,385,000 cells. The hemoglobin value remained about the same, i.e., 86 per cent. Four days after the blood examination, on August 7, the patient's fatal illness began, with symptoms of headache and sore gums. On August 14, one week after the onset, two teeth were extracted. As has been pointed out by others,[13] a history of the extraction of teeth has been obtained in some patients and is of considerable significance in the etiology of agranulocytic angina. Though in our patient the fatal illness had already started before this, it was observed that his condition became much worse following the extraction. It was at this time that the patient was then given fairly large doses of drugs containing acetphenetidin. Following his admission to the hospital the white cell count was found to be 350 and few granular cells were seen on the smear. The red cell count had fallen further, to 3,490,000 cells. The patient presented a typical picture of agranulocytic angina. The blood transfusion resulted in an increase of the red cell count to 4,380,000. The white cell count rose to 1350 cells, possibly as the result of adenosine sulfate therapy, and showed but few granular cells on smear examination. As the patient's condition became worse the white cell count diminished and on the day of death fell to 300 cells.

We have been unable to find any report in the literature in which a persistent and practically asymptomatic leukopenia of unknown etiology and of this degree and duration was followed by the development of a typical and fatal agranulocytic angina. Minter [14] mentioned the case of a girl who had been

known to have a granulocytopenia of three years' duration, during which time the highest white cell count was 1700 and the highest percentage of polymorphonuclear leukocytes 32 per cent. At the end of this period agranulocytosis developed and the white cell count fell to 400, with 16 per cent polymorphonuclear leukocytes. The patient recovered with treatment, the white cell count rising to 4100, with 52 per cent polymorphonuclear leukocytes.

A depletion of available leukocytes in the blood-stream has been found even before the symptoms of agranulocytic angina start, and makes the organism more liable to severe infection. Severe infections may be an occasional cause of agranulocytosis but rarely give rise to the latter unless some underlying bone marrow dyscrasia is present.[3] The bone marrow has been considered a primary rather than a secondary factor in the production of agranulocytosis.[12] Jackson and Parker,[3] in reference to a report in the Journal of the American Medical Association on the importance of amidopyrine in the production of granulocytopenia, state that "the report does not say nor does it imply that all cases are due to the drug nor does it preclude the possibility that there may be some pre-existing bone marrow dyscrasia which affords a fulcrum upon which the drug may work." The latter half of this statement is strongly supported by the findings of a chronic and marked leukopenia in our patient. As to whether sepsis in our patient was the cause or the result of the agranulocytosis it is difficult to say. Either the course of the disease would have been the same regardless of whether acetphenetidin-containing drugs were taken or it may be said that the ingestion of these drugs hastened and intensified the severity of the illness.

Conclusion

1. A case report is presented in which a chronic and asymptomatic leukopenia of four and a half years' duration and of unknown etiology terminated fatally in typical agranulocytic angina.
2. The onset of the fatal illness was independent of any drug ingestion.
3. The case presented strongly supports the theory that agranulocytic angina tends to occur in one in whom a bone marrow dyscrasia is already present, resulting in a diminution of the granular cells in the peripheral blood stream.

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11. Heck, F. J.: Recurrent granulocytopenia, Proc. Staff Meet. Mayo Clin., 1934, ix, 200.
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EDITORIAL

ADVANCES IN CONTROL OF YELLOW FEVER

THE discovery by the American Commission in 1900 that yellow fever is caused by a filtrable virus and that it is conveyed by the bite of the mosquito, *Aëdes aegypti*, largely determined the methods used to control this disease during the subsequent three decades. Yellow fever was known to persist in endemic form in a number of maritime centers in tropical America, but it was not known to exist outside of these foci in interepidemic periods. The successful eradication of the disease from Havana and Panama and later from other cities by rigid anti-aegypti control measures led naturally to the hope that by extending such measures to all known endemic foci the disease might be eradicated from this continent. No other vector of the disease had been discovered, and it was not known to attack any other animal. This hope was shared by the members of the International Health Division of the Rockefeller Foundation when they started the campaign against yellow fever more than ten years ago.

For a short time it appeared that their efforts had been nearly successful. However, occasional cases of yellow fever appeared in unexpected places which could not readily be explained. Finally, Soper et al. (1933) [1] reported an epidemic in rural areas of Espirito Santo, Brazil, a region in which *A. aegypti* does not exist. An intensive study was then begun by this group to determine the extent of this new epidemiological type of yellow fever. They relied mainly on two procedures. First, they attempted by means of a viscerotome to get a small specimen of liver tissue from every individual in the district who died of any acute illness of less than 10 days' duration. The changes in the liver in yellow fever are believed to be pathognomonic. Secondly, they examined the blood of large numbers of individuals for antibodies by the mouse protection test. Such antibodies appear in the plasma and apparently persist throughout life in patients who recover.

These studies showed that yellow fever was endemic in many widely scattered areas throughout the interior of Brazil and several adjacent South American countries in which it had not previously been recognized. The disease tends to appear as scattered cases or in small epidemics in areas in or adjacent to forests or uncleared land. Hence it was termed jungle yellow fever. The sparsity of human cases in some of these areas indicated that man can not be the primary reservoir of the infection. This must be sought in the wild animals of the jungle, probably in the monkeys. These are susceptible to infection experimentally, and in these regions from 20 to 25 per cent of the monkeys may show antibodies in their serum. Man does not constitute an essential part of this cycle, and is only incidentally affected.

[1] SOPER, F. L., et al: Yellow fever without *Aëdes aegypti*. Study of a rural epidemic in the Valla do Chanaan, Espirito Santo, Brazil, Am. Jr. Hyg., 1933, xviii, 555.

A search for other vectors showed that many other species of mosquitoes and also certain ticks can convey the disease under experimental conditions. Individuals of three other species of mosquitoes, caught in the jungle, were found naturally infected with yellow fever virus.

The jungle yellow fever virus is identical with the ordinary virus in every respect except in the mode of its transmission. A man who acquires the disease in the jungle can infect *A. aegypti*, and be the starting point of an epidemic of the ordinary type. In both types of infection it is now known that a large majority of the cases of yellow fever are so mild that they are not recognized. After an epidemic as many as 70 per cent of the inhabitants of a locality may show antibodies in their blood, although few of them give a history of yellow fever.

These discoveries in no way lessen the importance of anti-aegypti measures, for this mosquito is still the most dangerous carrier as far as major urban epidemics are concerned. They do indicate the impossibility of eradicating the disease in this way, since effective anti-mosquito measures are impracticable in the jungle. An attempt to increase human resistance by vaccination appeared to be a more feasible procedure.

Shortly after the discovery by Stokes, Brown and Hudson that monkeys can be infected with yellow fever, Hindle (1928) [2] prepared a vaccine by treating the liver of infected monkeys with formol or phenol. Monkeys could be immunized with this material, but it was later shown that either the monkeys suffered an attack of yellow fever (from which they usually recovered), or the material was entirely inert.

The fact that only a living virus is effective as a vaccine against yellow fever introduces into the procedure a number of dangers which must be guarded against. The vaccine might cause an attack of yellow fever, or of encephalitis if a neurotropic strain is employed. If an attenuated virus is used, it might unexpectedly recover its original virulence. Also, the virus might get into the blood, and by infecting *A. aegypti* mosquitoes start an epidemic of the disease. The principal measures relied on to avoid these dangers are attenuation of the virus by various methods, the administration of immune serum with the vaccine, or both.

In 1931 Sawyer, Kitchen and Lloyd [3] first used suspensions of infected mouse brain (Theiler's neurotropic virus) and human immune serum in vaccinating 56 individuals in New York, with satisfactory results. This method was also employed successfully by Findlay [4] in London, who by 1938 had vaccinated 5,700 Europeans who were going to infected areas in Africa. No case of yellow fever is known to have occurred among them, although about 40 cases were reported from non-immunized Europeans in the same districts.

[2] Hindle, E.: A yellow fever vaccine, Brit. Med. Jr., 1928, i, 976.

[3] Sawyer, W. A., Kitchen, S. F., and Lloyd, W.: Vaccination against yellow fever with immune serum and virus fixed for mice, Jr. Exper. Med., 1932, lv, 945.

[4] Findlay, G. M.: Immunization against yellow fever, Trans. Roy. Soc. Trop. Med. and Hyg., 1934, xxvii, 437.

Meanwhile Lloyd, Theiler and Ricci [5] showed that the virus can be grown in cultures containing mouse embryo tissue and that such virus lost its viscerotropic properties but showed no increase in its neurotropism. This was substituted for the suspension of infected mouse brain, and in 1938 Soper and Smith [6] reported the results obtained by the use of this vaccine combined with immune serum. Like Findlay, they obtained satisfactory results with human immune serum, in that reactions were usually mild and that 35 of 37 cases tested had been immunized. However, the difficulty in getting adequate amounts of human immune serum would preclude using this method on a large scale. When they employed immune animal sera, difficulties were encountered in that either reactions were severe or many individuals failed to develop immunity.

Because of these difficulties recent efforts have been concentrated on methods of vaccination not requiring the use of immune serum. In 1933 Sellards and Laigret [7] had reported using live neurotropic mouse brain virus in man. In the first six cases the results were satisfactory, but of seven later cases, severe reactions occurred in two. Laigret [8] then devised a method of progressively attenuating the vaccine, and administered three doses of increasing virulence to 3000 individuals in French West Africa. Of these a third had more or less marked reactions and two showed symptoms of encephalitis or myelitis. Findlay also tried the use of an attenuated virus in monkeys, but concluded it was dangerous to use it in man without serum.

More success, however, attended the efforts of the Rockefeller Foundation group. They found that after prolonged cultivation in chick embryo from which the brain and spinal cord had been removed, the virus lost all of its viscerotropic and most of its neurotropic properties. It still caused encephalitis on intracerebral injection into mice, although the incubation period was prolonged. It would no longer do this in monkeys. On ordinary injection into monkeys (without immune serum) it either caused no clinical evidences of illness or at most a slight febrile reaction, yet it regularly induced complete immunity to subsequent injection of highly virulent strains of virus. This was associated with the appearance of protective substances in the blood.

Based on these observations, vaccination experiments were undertaken on human volunteers in small carefully studied groups, first in New York (Theiler and Smith, 1937) and later in Brazil by the Coöperative Yellow Fever Service. A single dose of this chick embryo virus was given without serum. As highly satisfactory results were obtained in the preliminary

[5] Lloyd, W., Theiler, M., and Ricci, N. I.: Modification of the virulence of yellow fever virus by cultivation in tissues in vitro, Trans. Roy. Soc. Trop. Med. and Hyg., 1936, xxix, 481.

[6] Soper, F. L., and Smith, H. H.: Yellow fever vaccination with cultivated virus and immune and hyperimmune serum, Am. Jr. Trop. Med., 1938, xviii, 111.

[7] Sellards, A. W., and Laigret, J.: Vaccination de l'homme contre la fièvre jaune, Compt. Rend. Acad. Sci., 1932, cxciv, 1609.

[8] Laigret, J.: La vaccination contre le fièvre jaune, Bull. Soc. Path. Exot., 1933, xxvi, 806.

trials, it was applied on a wider scale, and in 1938 Smith, Penna and Paoliello [9] reported their results on 59,532 cases vaccinated during 1937. In October, 1938, Soper [10] reported that 800,000 persons had been vaccinated during the preceding nine months, with equally satisfactory results, at a cost of between eight and nine cents each.

The vaccine in most cases caused no appreciable reaction. In from 15 to 25 per cent of the cases there was headache, and less frequently slight fever, weakness and grip-like pains, coming usually on the sixth or seventh day. In about 1.5 per cent or less the reaction may be incapacitating for a day or two. No alarming reactions and no cases of encephalitis have been observed.

Virus in low concentration has been found in the blood in a minority of the cases when tested by intracerebral injections into mice. However, attempts by Whitman (1939) to infect *A. aegypti* and transmit the infection from such cases were not successful. Peltier et al. (1939) were also unable to do this in vaccinated cases in French West Africa. The risk of starting an *A. aegypti* borne epidemic from vaccinated persons would therefore seem to be practically negligible.

As judged by protection tests on sample groups, immunity developed in from 90 to 95 per cent of the cases. If cases which received inert vaccine are eliminated, the number protected rises to from 95 to 97 per cent. Immune bodies do not begin to appear until after eight or nine days and are regularly present by the twenty-first day. They have persisted in practically all cases tested for a year, but often in reduced concentration. The duration of the immunity has not been determined. Animal and human experiments indicate that protection is afforded as long as antibodies persist. How long this will be and whether protection will outlast demonstrable serum antibodies is not yet known. The practical value of vaccination from the epidemiological standpoint can be determined only after a much longer period of observation. That protection is substantial is indicated by the fact that since the vaccination of the laboratory personnel was instituted no case of yellow fever has occurred among them, whereas before this deaths were distressingly frequent—including Stokes, Noguchi, Young, Lewis, and Hayne. As carried out at present in expert hands the procedure promises to be comparable in safety and effectiveness to vaccination against smallpox. Universal vaccination in the vast areas involved will be a colossal task, yet it would not be an excessive price to pay for the control of this scourge if its effectiveness on a large scale is demonstrated.

P. C.

[9] SMITH, H. H., PENNA, H. A., and PAOLIELLO, A.: Yellow fever vaccination with cultured virus (17 D) without immune serum, Am. Jr. Trop. Med., 1938, xviii, 437.

[10] SOPER, F. L.: Yellow fever: the present situation (October, 1938) with special reference to South America, Trans. Roy. Soc. Trop. Med. and Hyg., 1938, xxvi, 297.

REVIEWS

Diseases of the Skin. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (Edin.), and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (Edin.). 1549 pages; 26 × 18 cm. Tenth Edition. C. V. Mosby Company, St. Louis. 1939. Price, $15.00.

The recently issued tenth edition of Sutton and Sutton's *Diseases of the Skin* includes some mention of all the more recent important contributions to dermatologic literature. The new volume is an excellent reference text. The print and the illustrations are very good.

While this book is admittedly one of the best textbooks on dermatology in the English language the reviewer is disappointed to find in this new edition many of the defects which have detracted from its value in the past.

The authors devote too much space to personal and unproved theories. This is especially true in the parts dealing with the treatment of acne and with carcinoma of the skin.

The use of the term eczema is still as confused as in earlier editions; eczema rubrum, sclerosum, squamosis and other forms of clinical eczema are described which have no real nosologic significance. Contact dermatitis is termed contact eczema in some places.

The authors state that their section dealing with syphilis is sketchy. In addition it may be stated that it is inadequate and that the treatment routines recommended are in many instances not in accord with modern standards.

In summary, this excellent volume is badly in need of further revision.

F. A. E.

The Art of Anaesthesia. By PALUEL J. FLAGG, M.D. 491 pages; 23.5 × 16 cm. Sixth Edition Revised. J. B. Lippincott Company, Philadelphia. 1939. Price, $6.00.

This is a well illustrated volume, in which a survey of the subject is given in an elementary but practical manner.

The newer anaesthetic agents, such as cyclopropane, divinyl ether and avertin, are discussed, in addition to the newer local and intravenous ones. An adequate discussion is given of the problem of dental anaesthesia.

The value of helium and carbon dioxide and the technics for their use are discussed. Oxygen therapy is mentioned and stressed; however, detailed discussion is lacking.

A very satisfactory description is given of the indications for and methods of intratracheal anaesthesia and the apparatus used.

The book is comprehensive in its scope. There is no attempt made to discuss the theory and physiology of anaesthesia. It should be found to be of considerable practical value.

Discrepancies noted in references to various pages and in the index do not interfere with the basic value of the book.

G. H. Y.

Clinical Toxicology. By CLINTON H. THIENES, M.D., PH.D. 309 pages; 20.5 × 14 cm. Lea and Febiger, Philadelphia. 1940. Price, $3.50.

A modern, pleasantly bound textbook of toxicology that deals with common poisons in a brief and direct manner. Differential symptomatology and pathology of

similar compounds are well brought out. The section on anesthetics and their impurities is to the point. Treatment, symptoms, diagnosis, and chemical identification are helpfully outlined. Tabulation of section outlines might be more convenient and cross reference to page number instead of chapter number would be helpful. Recommendation of sedatives to control tetanus convulsions is not in line with Howell's newer findings, but the book on the whole is up to date. It includes the toxicology of sulfanilamide. Tests for common poisons are briefly given.

C. A.

Peripheral Vascular Diseases: Diagnosis and Treatment. By WILLIAM S. COLLENS, B.S., M.D., and NATHAN D. WILENSKY, M.D. 243 pages; 25 × 16 cm. Charles C. Thomas, Springfield, Illinois. 1939. Price, $4.50.

This is a compact and rather comprehensive survey of the more common vascular disturbances. It should be valuable from the viewpoint of correlating diagnosis, management and treatment of these diseases.

The more usual types of vascular disturbances, such as arteriosclerosis, thromboangiitis obliterans and Raynaud's disease, are discussed in detail. Old methods of treatment, as well as the most recent, are described. Suggestions are given as to the management of these conditions, e.g., medically, from the supportive viewpoint and also physio-therapeutic.

The value of vascular, sympathetic and nerve surgery is reviewed.

Diagnostic signs and symptoms are described. In attempting to maintain a practical tone to the book, physiology is not stressed.

For a book attempting to be comprehensive in scope, an undue amount of space is given to one specific form of therapy, e.g., intermittent venous occlusion. This is particularly true when it is realized that this method, similar to other physio-therapeutic measures, is limited in scope and that the status of any one method has not been firmly established.

This book should be valuable as a guide to the individual in private practice.

G. H. Y.

COLLEGE NEWS NOTES

Committee on Nominations—1940–41

In accordance with provisions of the Constitution, President James D. Bruce has announced the appointment of the following Committee on Nominations for the coming year:

David P. Barr, St. Louis, Mo., *Chairman*
Reginald Fitz, Boston, Mass.
Fred M. Smith, Iowa City, Iowa
Charles F. Tenney, New York, N. Y.
Ernest B. Bradley, Lexington, Ky.

Drs. Barr and Fitz are selected from the Board of Regents; Drs. Smith and Tenney from the Board of Governors; Dr. Bradley from the membership at large.

The duties of the Committee on Nominations are to nominate candidates for the elective offices, Board of Regents and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective States, Provinces or districts which will be represented by the nominees, if elected. The list of nominees for President-Elect and for the First, Second and Third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its Annual Business Meeting. This does not preclude nominations made from the floor at the annual meeting itself.

The Election of the American College of Physicians to Membership in the United States Pharmacopoeial Convention

At the thirteenth decennial meeting of the United States Pharmacopoeial Convention, held at Washington, D. C., May 14 and 15, 1940, under the Presidency of Dr. Walter A. Bastedo, F.A.C.P., New York City, the American College of Physicians was elected a member of the Convention and its delegates, Dr. Torald Sollmann, F.A.C.P., Cleveland, Dr. Charles F. Tenney, F.A.C.P., New York City, and Dr. Edward D. Spalding, F.A.C.P., Detroit, were seated. Dr. Sollmann was elected Chairman of the College delegation and during the meeting was appointed to the Committee on Constitution and By-Laws of the Convention.

The Convention was reported to be one of the most harmonious, democratic and progressive of the Pharmacopo ial Conventions held to date. It made provision for adapting the Pharmacopoeia to the accelerated tempo of the present time. It also instructed the Trustees to appoint a committee to plan such further and more radical changes as may be advisable, and to report within two years to a special meeting of the Convention.

New Officers elected were:

President—Dr. C. W. Edmunds, Ann Arbor, Mich.
First Vice President—H. A. B. Dunning, Baltimore, Md.
Second Vice President—Dr. Cary Eggleston, New York, N. Y.
Third Vice President—George Moulton, Peterborough, N. H.
Fourth Vice President—Dr. H. C. Wood, Jr., Philadelphia, Pa.
Fifth Vice President—Robert C. Wilson, Athens, Ga.
Secretary—L. E. Warren, Chevy Chase, Md.
Assistant Secretary—Frank Delgado, Washington, D. C.
Treasurer—W. Paul Briggs, Washington, D. C.

Dr. Walter A. Bastedo, retiring President, became Vice Chairman of the Board of Trustees. Of the fifty-one members on the Committee on Revision, eighteen are from the medical profession, of whom the following are Fellows of the American College of Physicians:

Dr. Walter A. Bastedo, New York, N. Y.
Dr. Charles L. Brown, Philadelphia, Pa.
Dr. William B. Castle, Boston, Mass.
Dr. Arthur C. DeGraff, New York, N. Y.
Dr. George W. McCoy, Washington, D. C.
Dr. Virgil E. Simpson, Louisville (Vice Chairman)
Dr. Soma Weiss, Boston, Mass.

Gifts to the College Library

Acknowledgment is made of the receipt of the following reprints by members of the College:

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R.—1 reprint;
Dr. Paul A. Draper, F.A.C.P., Colorado Springs, Colo.—1 reprint;
Dr. Everett C. Fox, F.A.C.P., Dallas, Tex.—1 reprint;
Dr. Lawrence E. Geeslin (Associate), Atlanta, Ga.—5 reprints;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—bound volume of reprints;
Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif.—*2* reprints;
Dr. John H. Musser, F.A.C.P., New Orleans, La.—*27* reprints;
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;
Dr. Marjorie E. Reed, F.A.C.P., Plymouth, Pa.—*2* reprints;
Dr. Joseph Rosenfeld, F.A.C.P., Youngstown, Ohio—1 reprint;
Dr. Merritt H. Stiles, F.A.C.P., Philadelphia, Pa.—*2* reprints.

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, was appointed May 18, 1940, a member of the Committee on Advertisements and Commercial Exhibits of the American College of Physicians, filling the vacancy caused by the resignation of Dr. William D. Stroud, F.A.C.P. Dr. Stroud had served some years on this Committee and had made a real contribution, especially in connection with the new regulations governing the admission of commercial exhibits.

At the annual meeting of the Austen Riggs Foundation, Inc., held in Stockbridge, Mass., on May 11, 1940, Dr. Horace K. Richardson, F.A.C.P., was elected Medical Director of the Foundation, succeeding Austen Fox Riggs, F.A.C.P., who died on March 5, 1940.

Dr. Juan A. Pons, F.A.C.P., San Juan, P. R., has resigned as Assistant Professor of Medicine at the School of Tropical Medicine of Puerto Rico and is now engaged in private practice and head of the medical service of the Presbyterian Hospital, San Juan.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Nutrition and Deficiency Disease, with Special Reference to Vitamins" before the Cumber-

land County Medical Society at Portland, Maine, on April 25. He also presented a paper on "Factors Involved in Digestion and Absorption in Deficiency Disease" before the annual postgraduate lectures of the Attending Staff of Mercy Hospital, Philadelphia, May 13, 1940.

Dr. August A. Werner, F.A.C.P., St. Louis, Mo., delivered two addresses under the auspices of the Postgraduate Committee of the Iowa State Medical Society at Marshalltown, Iowa, May 7, and at Ames, Iowa, May 8. The title of the addresses was "The Anterior Pituitary Gonad Relationship in the Female." Dr. Werner also addressed the Central District Medical Society, Davenport, Iowa, May 16, on the same subject.

The Sixteenth Scientific Sessions of the American Heart Association were held in New York City, June 7–8, 1940, under the presidency of Dr. William D. Stroud, F.A.C.P., Philadelphia. Dr. William Goldring, F.A.C.P., New York, was chairman of the program committee. Twenty-eight papers appeared on the four sessions and twenty-three of the contributors were either Fellows or Associates of the American College of Physicians.

A cardiovascular exhibit was held under joint auspices of the American Heart Association and the American Medical Association. Among the exhibitors were the following:

Radiology and Pathology of Heart Disease, Dr. Hugo Roesler, F.A.C.P., Philadelphia;

The Effect of Tobacco Smoke and Nicotine Upon the Normal Heart and Upon the Heart with Myocardial Infarction: An Experimental Study on Dogs, Dr. Samuel Bellet (Associate), Philadelphia;

Salient Public Health Features of Rheumatic Heart Disease, Dr. O. F. Hedley, F.A.C.P., Philadelphia;

The Fluoroscopic Diagnosis of Cardiac Infarction Following Coronary Artery Occlusion, Dr. Arthur M. Master, F.A.C.P., Dr. Richard Gubner and Arthur Grishman, New York;

Venous Pressure Studies in Cardiovascular and Peripheral Vascular Diseases, Dr. J. Ross Veal and Dr. Hugh Hussey (Associate), Washington, D. C.;

Cardiovascular Disease in Advanced Years, Dr. Louis B. Laplace, F.A.C.P., Philadelphia;

Experimental Endocarditis Induced by Intravenous Inoculation of Streptococcus Viridans, Dr. W. J. MacNeal, F.A.C.P., Dr. Martha Spence and Dr. Marie Wasseen, New York;

(*A*) Lymphedema. (*B*) Deproteinated Pancreatic Extract in the Treatment of Intermittent Claudication, Dr. A. Wilbur Duryee, F.A.C.P., and Dr. Gerald H. Pratt, New York;

Diagnostic Procedures in Peripheral Arterial Disease, Dr. Hugh Montgomery (Associate), Dr. Meyer C. Naide and Dr. Norman E. Freeman, Philadelphia;

Plethysmographic Method for the Study of Blood Flow and Vascular Responses in the Extremities, Dr. David I. Abramson, F.A.C.P., and Dr. Fanny Senior, Cincinnati;

Classification of "Essential" Hypertension, Dr. Henry A. Schroeder (Associate), New York;

Cine-roentgenographic Studies of the Human Pulmonary Circulation, Heart Chambers and Greater Blood Vessels (Robb and Steinberg Method), Dr. William H. Stewart, F.A.C.P., and Dr. Charles W. Breimer, New York.

Under the sponsorship of the Florida Medical Association, in coöperation with the Florida State Board of Health, the eighth annual graduate short course for doctors of medicine was offered at Jacksonville, June 24–29. On a six-day program, five hours were given to Pediatrics, five hours to Gynecology, six hours to Obstetrics, four hours to Venereal Diseases, six hours to Surgery, three hours to Orthopedic Surgery and six hours to Medicine. In addition, there was a special dinner and round table for Surgery and one for Medicine. Dr. Henry M. Thomas, F.A.C.P., Associate in Medicine, Johns Hopkins University School of Medicine, presented the courses in Medicine and conducted the medical round table. Dr. T. Z. Cason, F.A.C.P. and College Governor for Florida, Jacksonville, was chairman of the postgraduate committee. A shorter postgraduate program or graduate seminar of three days was also offered under the same auspices for Negro doctors of medicine.

The forty-third annual meeting of the American Gastro-enterological Association was held at Atlantic City, June 10–11, 1940, under the Presidency of Dr. Irvin Abell, F.A.C.S., Louisville, Ky. Among Officers of the organization are Dr. Andrew C. Ivy, F.A.C.P., Chicago, First Vice-President; Dr. Russell S. Boles, F.A.C.P., Philadelphia, Second Vice-President; Dr. A. F. R. Andresen, F.A.C.P., Brooklyn, Secretary; Dr. A. H. Aaron, F.A.C.P., Buffalo, Treasurer; Dr. Sara M. Jordan, F.A.C.P., Boston, Recorder. Dr. Chester M. Jones, F.A.C.P., Boston, and Dr. Ernest H. Gaither, F.A.C.P., Baltimore, are members of the Council; Dr. Albert M. Snell, F.A.C.P., Rochester, Minn., and Dr. Walter L. Palmer, F.A.C.P., Chicago, are members of the Committee on Admissions and Ethics.

Twenty-six individual presentations, dealing with Gastro-enterological subjects, were made, sixteen of the contributors being either Fellows or Associates of the American College of Physicians. Examination of the membership list of the Society reveals that of thirty-three senior members, twenty-six are Masters, Fellows or Associates of the American College of Physicians; of the one hundred and sixteen active members, seventy are Fellows or Associates of the College; of eighteen associate members, eleven are Fellows of the College; or, of a total membership of one hundred sixty-seven, one hundred and seven (or 64 per cent) are members of the American College of Physicians.

Emory University Alumni Clinic Week was held in the medical building of the School of Medicine, Atlanta, June 4–7. All white physicians, regardless of the medical school from which they graduated, were invited to attend, and there was no fee or charge made. The clinic week is held under the auspices of the physicians of the Fulton County Medical Society and Emory University. Clinics were conducted primarily by Atlanta physicians from Tuesday through Friday. Twenty Fellows or Associates of the College participated in the clinic program.

Dr. Everett C. Fox, F.A.C.P., Dallas, Tex., was recently elected President of the Dallas Southern Clinical Society.

Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., addressed the 69th annual session of the California Medical Association, held in Coronado May 6–9, on "Endocrinology: A Critical Appraisal."

The Connecticut State Medical Society held its 148th annual meeting in Hartford, May 22, under the presidency of Dr. Joseph I. Linde, F.A.C.P., New Haven. Guest speakers on the general program included Dr. William S. McCann, F.A.C.P., Rochester, N. Y., and Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa.

Dr. Paul D. White, F.A.C.P., Boston, Mass., was the guest speaker at a meeting of the Hezekiah Beardsley Pediatric Club.

Among Fellows of the College who addressed the 149th annual meeting of the New Hampshire Medical Society, held in Manchester May 14–15, were:

Dr. Elliott P. Joslin, Boston, Mass.—" Diabetic Hazards and How to Meet Them ";
Dr. Priscilla White, Boston, Mass.—" Diabetes in Children and Adolescents: Problems and Management; Pregnancy in the Diabetic ";
Dr. Alexander Marble, Boston, Mass.—" Diet and Insulin ";
Dr. Cornelius P. Rhoads, New York, N. Y.—" Vitamins ";
Dr. Nathan B. Van Etten, New York, N. Y.—" The Education of the Intern."
Dr. Van Etten later addressed the society banquet on " An American Health Program."

The 53rd annual meeting of the North Dakota State Medical Association was held in Minot May 6–8, under the presidency of Dr. Harry A. Brandes, F.A.C.P., Bismarck. Dr. Charles N. Hensel, F.A.C.P., St. Paul, Minn., presented a symposium on essential hypertension and Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn., spoke on " The Eczemas."

The Ohio State Medical Association held its 94th annual meeting in Cincinnati May 14–16. Among the speakers at the general sessions of this meeting were:

Dr. William Osler Abbott (Associate), Philadelphia, Pa.—"The Rôle of Small Intestinal Intubation in the Treatment of Intestinal Obstruction and in the Diagnosis of Obstructing Lesions ";
Dr. Raymond A. Ramsey (Associate), Columbus, Ohio—" Treatment of Disorders of the Thyroid ";
Dr. Sidney E. Wolpaw (Associate), Cleveland, Ohio—" Diagnosis of Early Pulmonary Tuberculosis."

The Oklahoma State Medical Association held its 48th annual session in Tulsa May 6–8. Guest speakers at the general scientific sessions included Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn.—" Tuberculosis and the General Practitioner; Medical Aspects of Child Behavior," and Dr. Alphonse McMahon, F.A.C.P., St. Louis, Mo.—"Effect of Aminophylline on the Electrocardiogram; Group Hospital Insurance."

Dr. McMahon, Vice President of the American Medical Association, spoke at an evening general meeting on " The Medical Profession, Its Aims and Responsibilities." During this meeting Dr. Henry H. Turner, F.A.C.P., Oklahoma City, was installed as president of the Association.

Dr. Horton R. Casparis, F.A.C.P., Nashville, Tenn., spoke on " Recent Advances in Chemotherapy " and " Recent Attitudes Toward Thymic Conditions "; and Dr.

James G. Hughes (Associate), Memphis, Tenn., spoke on "The New Tuberculin Patch Test" at the annual meeting of the Oklahoma Pediatric Society, May 6, at Tulsa.

Among the guest speakers on the scientific program of the general meetings of the 74th annual session of the Texas State Medical Association, held in Dallas, May 14–16, were:

Dr. Frank J. Heck, F.A.C.P., Rochester, Minn.—"Iron Requirements in Childhood and Adult Life";
Dr. Alan Brown, F.A.C.P., Toronto, Ont.—"A Consideration of Some Common Pediatric Problems";
Dr. Arthur C. Christie, F.A.C.P., Washington, D. C.—"Diagnosis and Management of Cancer of the Breast."

Dr. William L. Powers (Associate), Wichita Falls, Dr. Walter G. Reddick, F.A.C.P., Dallas, and Dr. William S. Horn, F.A.C.P., Fort Worth, were among those who spoke at a symposium on sulfanilamide therapy. Among the speakers at the symposium on hematology were Dr. William Boyd Reading, F.A.C.P., Galveston, Dr. Alvis E. Greer, F.A.C.P., Houston, and Dr. Moise D. Levy, F.A.C.P., Houston.

Under the presidency of Dr. James H. Hutton, F.A.C.P., Chicago, the Illinois State Medical Society held its 100th annual meeting in Peoria, May 21–23. Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, spoke on "Selection of Cases of Splenectomy," and Dr. Tom D. Spies, F.A.C.P., Cincinnati, Ohio, spoke on "Diagnosis and Treatment of Common Deficiency Diseases in the Adult."

The oration in medicine was delivered by Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa. His subject was: "The Rôle of the Kidney in Cardiorenal-Vascular Disease."

The University of Chicago announced that Dr. Anton J. Carlson, F.A.C.P., who is professor and Chairman of the department of physiology, Division of Biological Sciences, will become emeritus professor at the end of the current year.

The following members of the College were among the speakers at the 81st annual session of the Kansas Medical Society held in Wichita, May 13–16:

Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich.—"Treatment of Edema";
Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill.—"Treatment of Chronic Indigestion";
Dr. Soma Weiss, F.A.C.P., Boston, Mass.—"Cardiac Asthma and Pulmonary Edema";
Dr. Daniel V. Conwell, F.A.C.P., Halstead, Kan.—"A Clinical Approach to the Migraine Problem—Preventive Treatment";
Dr. Aaron A. Sprong (Associate), Sterling, Kan.—"Radiation of Leukemia."

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., spoke on "Treatment of Pneumococcal Pneumonia," and Dr. Thomas Parran, F.A.C.P., Washington, D. C., spoke on "The Public Health Aspects of Syphilis as It Concerns the General Practitioner" at the 159th annual meeting of the Massachusetts Medical Society in Boston, May 21–22.

At a symposium on sulfanilamide Dr. Conrad Wesselhoeft, F.A.C.P., Boston, spoke on "Management of Acute Streptococcal Infections of the Upper Respiratory Tract," and Dr. Chester S. Keefer, F.A.C.P., Boston, spoke on "Diagnosis and Treatment of Gonorrheal Arthritis."

The New Mexico Medical Society held its annual session in Albuquerque, May 27–29. Among the Fellows of the College who spoke at this meeting were:

Dr. Ray M. Balyeat, Oklahoma City, Okla.—"Diagnosis and Treatment of the Common Allergic Manifestations as Seen by the General Practitioner";
Dr. Albert Soiland, Los Angeles, Calif.—"Further Notes on the Clinical Aspect of Ultra Short Wavelength X-Rays";
Dr. Paul M. Bassel, Temple, Tex.—"Frequency of Spinal Cord Tumors and Their Diagnosis."

Dr. William McCully James, F.A.C.P., College Governor for the Republic of Panama and the Canal Zone, delivered the first James Carroll Flippin Memorial Lecture at the 25th semiannual postgraduate clinic presented by the University of Virginia Medical Department at Charlottesville, April 5–6.

At the recent annual meeting of the Federation of American Societies for Experimental Biology in New Orleans, La., Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., was elected president of the American Physiological Society, and Dr. Gustave P. Grabfield, F.A.C.P., Boston, Mass., was elected secretary of the American Society of Pharmacology and Experimental Therapeutics.

The 174th annual meeting of the Medical Society of New Jersey was held at Atlantic City, June 4–6, 1940. Among the guest speakers were:

Dr. Sydney R. Miller, F.A.C.P., Baltimore—"Chronic Nephritis and Its Treatment in the Light of Contemporary Renal Physiology";
Dr. William D. Stroud, F.A.C.P., Philadelphia—"Gastrointestinal Disturbances in Cardiovascular Disease";
Dr. Charles L. Brown, F.A.C.P., Philadelphia—"The Relation of the Anemias to Gastrointestinal Diseases";
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia—"Factors Involved in Digestion and Absorption in Deficiency Disease";
Dr. Charles C. Wolferth, F.A.C.P., Philadelphia—"Cardiovascular Symptomatology in Biliary Tract Drainage";
Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia—"Hyperinsulinism";
Dr. William A. Swalm, F.A.C.P., Dr. Lester M. Morrison (Associate), and Dr. Chevalier L. Jackson, Philadelphia—"Gastritis. Diagnosis and Treatment";
Dr. Samuel Bellet (Associate), Dr. Leon Schwartz (Associate), Dr. Alfred Kershbaum, and Dr. Richard H. Meade, Jr., Philadelphia—"The Effect of Tobacco Smoke and Nicotine Upon the Normal Heart and in the Presence of Myocardial Disease Produced by Coronary Artery Ligation: An Experimental Study in Dogs";
Dr. Thomas Fitz-Hugh, Jr., Philadelphia—"Gastrointestinal Disturbances in the Hemorrhagic Blood Dyscrasias."

Scientific Exhibits were entered by:

Dr. J. H. Clark, F.A.C.P., Dr. Albert Behrend, Dr. Helena E. Riggs, and Dr. Moses Behrend, Philadelphia—"Cerebral Complications Following Surgical Operations";

Dr. J. Russell Twiss, F.A.C.P., New York—"Biliary Colic: Etiology, Diagnostic Significance and Treatment";

Dr. William A. Swalm, F.A.C.P., Dr. Lester Morrison (Associate), and Dr. C. L. Jackson, Philadelphia—"Chronic Gastritis";

Dr. Herbert T. Kelly, F.A.C.P., Dr. Edmund L. Housel, and Dr. William M. Emrey, Philadelphia—"Deficiency Disease";

Dr. Louis L. Perkel, F.A.C.P., Jersey City—"Unusual Manifestations of Peptic Ulcer—Roentgen Demonstration."

There was a combined session on medicine and gastro-enterology, Dr. Thomas M. Kain, F.A.C.P., Camden, being chairman of the section on medicine and Dr. Hyman I. Goldstein (Associate), Camden, being chairman of the section on gastro-enterology. Dr. Clarence L. Andrews, F.A.C.P., Atlantic City, presented a paper on "Cardiovascular Disturbance in Gastrointestinal Diseases."

On the program of the combined session, pediatrics and radiology, Dr. William G. Bernhard (Associate), Newark, was one of the leaders in the discussion of diagnosis in connection with a symposium on "Blood Dyscrasias in Infancy and Childhood."

At the session on gastro-enterology, Dr. Manfred Kraemer, F.A.C.P., Newark, gave an address on "Common Diarrheas: Causes and Treatment"; Dr. Christopher C. Beling, F.A.C.P., Newark, gave a paper on "Gastrointestinal Disturbances in Neurological Disorders"; and Dr. D. Ward Scanlan, F.A.C.P., with Dr. Clarence Whims, both of Atlantic City, gave a paper on "Suppurative Cholangitis."

On the program of the section on medicine, Dr. John W. Gray, F.A.C.P., Newark, gave a paper on "The Management of Infected Tonsils, Teeth and Sinuses in Arthritis"; Dr. Thomas K. Lewis, F.A.C.P., Camden, gave a paper on "Résumé of Present-Day Treatment of Arthritis"; Dr. Ralph K. Hollinshed, F.A.C.P., Westville, a paper on "Coronary Artery Disease"; and Dr. Benjamin Saslow (Associate), Newark, a paper on "Complications of Diabetes."

Dr. Edward C. Rosenow (Associate), Rochester, Minn., addressed The California State Dental Association, May 14, on "The Prevention and Elimination of Infections In and About Teeth and Thereby of Systemic Disease."

Dr. Perry J. Melnick, F.A.C.P., Chicago, has been appointed pathologist to supervise a diagnostic service in connection with the establishment of a division of cancer control in the Illinois State Department of Health, in accordance with recently enacted laws. About $18,000 has been appropriated. The work will be largely educational, emphasizing early diagnosis and early treatment.

Dr. David J. Davis, F.A.C.P., Dean of the University of Illinois College of Medicine, Chicago, has been appointed chairman of an advisory board to the division of cancer control.

In memory of the late Dr. Bernard M. Fantus, F.A.C.P., the new outpatient clinics of the Cook County (Ill.) Hospital group were dedicated on April 19. Dr. Fantus was formerly the Director of Therapeutics at the Hospital and the creator of the "blood bank" for quick transfusions.

Just preceding the meeting of the American Medical Association in New York City, June 10–14, The New York Post-Graduate Medical School offered several intensive courses; June 3–7, "Clinical Interpretations of Laboratory Data" by Dr. Maurice Bruger (Associate); June 3–8, "Diseases of the Liver and Biliary Tract" by Dr. Carl H. Greene, F.A.C.P., Dr. John Russell Twiss, F.A.C.P., and Dr. Rupert Franklin Carter. Following the American Medical Association meeting a ten-day symposium on medicine was conducted under Dr. Walter G. Lough, F.A.C.P.

Dr. Thomas T. Mackie, F.A.C.P., New York City, addressed the American Proctologic Society at Richmond, Va., June 9–11, on "The Rôle of Avitaminosis in Rectal Bleeding."

Among guest speakers on the program of the annual meetings of the National Tuberculosis Association, the American Trudeau Society and the National Conference of Tuberculosis Secretaries at Cleveland, June 3–6, were:

Dr. Maxim Pollak, F.A.C.P., Peoria, Ill.—"Tuberculosis in Mental Institutions";
Dr. William H. Weidman (Associate), Norwich, Conn.—"The Application of Laminagraphy in Chest Conditions";
Drs. Richard M. McKean, F.A.C.P., George C. Thosteson, F.A.C.P., and Nathan Brooks, Detroit—"Treatment of Tuberculosis and Diabetes, A Ten Year Experience."

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, addressed a public meeting at Cincinnati, May 20, held in coöperation with the Cincinnati Academy of Medicine, Cincinnati Medical Hygiene Council and the Public Health Federation, his subject being "Alcoholism—A Personal and Social Problem." Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., presided.

The American Rheumatism Association held its annual meeting at New York City, June 10, under the presidency of Dr. Philip S. Hench, F.A.C.P., Rochester, Minn. Dr. Hench's presidential address was entitled, "Acute Multiple Recurring Arthritis and Periarthritis: Forty Cases of a New Articular Disease."

Dr. Julius L. Wilson, F.A.C.P., associate professor of medicine, Tulane University of Louisiana School of Medicine, New Orleans, was one of the lecturers in a series of postgraduate lectures in internal medicine, held at Montgomery, Ala., over a period of six weeks from April 26, for the benefit of physicians in nearby counties. The same lectures are to be repeated in other sections of Alabama.

Dr. Francis G. Blake, F.A.C.P., Sterling professor of medicine at Yale University School of Medicine, New Haven, has been appointed acting dean. Dr. Blake is a graduate of Harvard University School of Medicine, 1913, and served on the staff of Peter Bent Brigham Hospital until 1916, when he joined the Rockefeller Institute for Medical Research for a year. In 1917 he became associate professor of medicine

at the University of Minnesota Medical School and two years later became associate in medicine at Rockefeller Hospital. From 1920–21 he was associate member of the Rockefeller Institute and from 1924–35 he was a member of its scientific board of directors. In 1921 he became the John Slade Ely professor of medicine at Yale University and served until 1927 when he became Sterling professor of medicine. Dr. Blake has served as president of the American Society for Clinical Investigation and American Association of Immunologists. He was chairman of the division of medical sciences of the National Research Council from 1933–36 and chairman of the Section on the Practice of Medicine of the American Medical Association in 1938. He has been a Fellow of the American College of Physicians since 1930 and has served on its Board of Governors and on its Board of Regents.

Dr. Allen H. Bunce, F.A.C.P., Atlanta, has been made president-elect of the Medical Association of Georgia.

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, D. C., gave the fourteenth William Thompson Sedgwick Memorial Lecture of the Massachusetts Institute of Technology, April 11, on "Nutrition and the Nation's Health."

It was recently announced that Dr. Charles E. Stewart, F.A.C.P., director of the Battle Creek Sanitarium, Battle Creek, Mich., will retire at the end of the present year. He has been connected with this institution since 1895.

Dr. Frank J. Heck, F.A.C.P., Rochester, Minn., has been elected a vice president of the Minnesota State Medical Association.

Dr. James M. Flynn, F.A.C.P., Rochester, N. Y., was recently elected president of the Medical Society of the State of New York. Dr. Peter Irving, F.A.C.P., New York City, was reëlected secretary. This society will hold its 1941 meeting in Buffalo.

Dr. George Morris Piersol, F.A.C.P., Philadelphia, addressed the New York Academy of Medicine, May 2, on the general problem of aging.

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, College Governor for Wisconsin, addressed the Columbus (Ohio) Academy of Medicine recently on "Endocrine Therapy in General Practice."

Dr. Louis Hamman, F.A.C.P., Baltimore, has been elected president of the Association of American Physicians. Other officers included Dr. James H. Means, F.A.C.P., Boston, vice president, Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., secretary, and Dr. William S. McCann, F.A.C.P., Rochester, N.Y., treasurer.

OBITUARIES

DR. BERNARD FANTUS

Dr. Bernard Fantus died at his home in Oak Park, Illinois, on April 14, 1940, of hypertensive heart disease in his sixty-sixth year. He had been a Fellow of the American College of Physicians since 1919.

Dr. Fantus was born in Budapest, September 1, 1874. He attended the Real-Gymnasium in Vienna, came to America, continued his studies at the University of Illinois College of Medicine and received his M.D. degree in 1899. From 1902 to 1913 he was in charge of the Medical Dispensary at his alma mater. In 1908 he continued his postgraduate work at the University of Strasbourg and again in 1909 at the University of Berlin. He received a degree of Master of Science at the University of Michigan in 1917.

He was made Professor of Pharmacology and Therapeutics at the University of Illinois College of Medicine in 1903, which position he held until his death except for a period from 1924 to 1932 when he was Associate Professor of Medicine at Rush Medical College, teaching the clinical therapeutic courses which had previously been conducted by the well known Walter S. Haines.

Dr. Fantus' primary interest was in therapeutics. During the forty years of his practice he was the liaison officer between druggist and physician. The problems of coöperation between the two were laid at his door and received intelligent consideration. Druggists everywhere have remarked of late that "Pharmacy has lost its best friend in the medical profession." It was the intimate details of prescription writing and compounding which early received his attention. One is therefore not surprised that he was elected as a member of the Revision Committee of the United States Pharmacopoeia National Formulae and Recipe Book, nor that he was at all times actively participating in the affairs of the American Pharmaceutical Association. His books included works on prescription writing, candy medication, useful cathartics and the technic of medication. More recently he had been hard at work on The Therapy of the Cook County Hospital published from time to time in the Journal of the American Medical Association. His interest in the technic and art of medical therapeutics stimulated him to develop the Solutions Laboratory of the Cook County Hospital where he was director of Therapeutics. Special study was given to the reactions following intravenous administration of fluids. The exceedingly careful preparation of containers, solutions and tubing has resulted in almost complete absence of such reactions.

For twenty-two years Dr. Fantus acted as Editor of the Year Book of General Therapeutics, completing the 1939 edition just previous to his death. He was also editor of Merck's Manual and for twenty years edited the Digest of Therapeutics.

Dr. Fantus was the originator of the plan to form a convalescent park in the space between the Cook County Hospital, The Presbyterian Hospital, the Student YMCA and Rush Medical College. Through continued effort this large area has been cleared and planted. The new clinic building of the Cook County Hospital has been named in his honor.

From the layman's view the chief contribution of Dr. Fantus was in the establishment of the blood bank on March 15, 1937. This has been of inestimable value in an institution where the turn over is rapid and emergencies constantly at hand. No one acquainted with the situations constantly arising in large general hospitals doubts its value.

Dr. Fantus was a stimulating teacher. He inspired many younger men to investigate problems of therapeutics. He was interested in the health of the community. One of his last appearances was before a meeting of the Chicago Medical Society at which time he urged the society to broadcast the picture of acute appendicitis that the public might better appreciate the onset and symptoms of appendicitis, and the serious effects of delay and catharsis. He counseled the officers to spread the news by public education as has been done elsewhere.

He was a member of Phi Rho Sigma and Alpha Omega Alpha, of the Chicago Society of Internal Medicine as well as the American Medical Association, and the American Pharmaceutical Society. In 1933 he received the first honorary degree from the American Therapeutic Association for his work on more palatable mixtures of cod liver oil and castor oil.

Dr. Fantus is survived by his widow, his daughter and two brothers.

An inspiring teacher and practitioner who acquainted himself with the great details of the everyday problems of therapeutics has gone to his rest.

LeRoy H. Sloan, M.D., F.A.C.P.,
Governor of Northern Illinois

DR. EDWIN BOSWORTH McCREADY

Dr. Edwin Bosworth McCready, F.A.C.P., Pittsburgh, Pa., died November 3, 1939. He had been a Fellow of the College from 1917, and was Governor for western Pennsylvania for many years. During this term he was keenly active in plans for the future of the organization, and his counsel was most helpful.

Dr. McCready was born in Pittsburgh, the son of the late Robert J. McCready, M.D., and Delphine Bosworth McCready. His College training was received at Lafayette College, Easton, Pa., and the University of the South at Sewanee, Tenn. His medical training was received at Jefferson Medical College of Philadelphia, and the Medico-Chirurgical College of Philadelphia from which he graduated in 1903. He was a member of the Allegheny County Medical Society, Pennsylvania State Medical Society, the

American Medical Association and a past President of the American Therapeutic Society. For many years he was Director of the Mental Health Division of the Juvenile Court of Allegheny County, and Examining Psychiatrist at the Mayview Hospital and the Thorn Hill School for Boys.

Dr. McCready's work and papers on speech defects and variation from the normal mental and endocrine states are outstanding in these fields. He demonstrated by his work the superiority of medical psychologists over lay psychologists.

He was a member of the Calvary Episcopal Church, and is survived by his wife, Jessie Kyle McCready, and a daughter, Delphine Bosworth McCready.

CLEMENT R. JONES, M.D., F.A.C.P.,
Pittsburgh, Pennsylvania

DR. WALTER H. MacCRAKEN

Dr. Walter H. MacCraken, Dean Emeritus of the College of Medicine of Wayne University, passed away on March 3, 1940, after an illness of only two days.

Dr. MacCraken was born in Albion, New York, in 1870. He attended the old Benton Harbor College, where he received his A.B. degree. He received his M.D. degree from the University of Louisville. After internship, he practiced medicine for several years in Bowling Green, Kentucky, but in 1906 returned to the University of Louisville as an instructor.

In 1914 he accepted a professorship in the Detroit College of Medicine and became Dean in 1917. He held the position until 1935, when, because of an untimely illness, he resigned the deanship. During the period of his administration, Dr. MacCraken successfully guided the school through many difficulties. By his leadership the school maintained a Class A ranking among the medical schools of the United States and Canada—this during a period when many schools were discontinued because of low standards. This accomplishment is particularly noteworthy in view of the fact that as the Detroit College of Medicine and Surgery the school was an independent organization not a part of a university. Dr. MacCraken and his associates, however, recognized that the medical school should be a department of a university, and he was gratified when the Board of Education, after an interval during which the school was operated as a unit of the public school system, established the Faculty of Medicine as the medical department of Wayne University. This evolution gives the school the distinction of being the only municipally owned and controlled medical school in the country. Dr. MacCraken was beloved by his students because of his subtle witticisms and his informal teaching methods. He had the kindly, humorous and philosophical outlook so characteristic of the medical man of the old school.

He was a Fellow of the American College of Physicians, a member of the Detroit Academy of Medicine, the Saturday Night Club, the Wayne County Medical Society, the Michigan State and American Medical Associations, the American Ornithologists Union, the Association of Audubon Societies, the Wilson Ornithological Society and the American Museum of Natural History.

Dr. MacCraken's vocation was the preparation of the youth to be of the greatest service to humanity by the training of honest, conscientious physicians. His hobby was Natural History, and his avocation, Ornithology.

On April 1, 1940, a memorial service was held by the Faculty at the Wayne University School of Medicine. A Resolution was adopted and it was resolved that his death be recorded in the proceedings of the Committees on Administration and the Faculty Council of the College of Medicine, with sentiments of highest regard for his memory and a deep sense of loss on the part of his faculty colleagues.

Dr. MacCraken is survived by his wife Hattie, and a daughter, Dr Frances MacCraken, an Assistant Professor in the School of Medicine.

WILLIAM J. STAPLETON, JR., M.D., F.A.C.P.,
Associate Dean, Wayne University College of
Medicine, Detroit, Michigan

RECENT ANNOUNCEMENTS

Dr. Torald Sollmann, F.A.C.P., Dean of Western Reserve University School of Medicine, has announced that fellowships and scholarships have been awarded from the Crile Research Scholarship Fund for work at Western Reserve University during the summer as follows:

From the first-year class: two awards for work in the Department of Biochemistry and three awards for work in the Department of Anatomy;

From the second-year class: one award for work in the Department of Hygiene and Bacteriology, one award for work in Pathology, two awards for work in Physiology, one award for work in Pharmacology and one award for work in Biochemistry;

From the third-year class: one award for work in the Department of Hygiene and Bacteriology, one award for work in Surgery and one award for work in Pathology.

From Western Reserve University also comes the announcement that the John and Mary R. Markle Foundation of New York has appropriated $4,100 for the continuation of studies of the "cause and treatment of ventricular fibrillation." The studies have been in progress for a year in the School of Medicine under the direction of Dr. Carl J. Wiggers, F.A.C.P., Professor of Physiology.

President Winfred G. Leutner of Western Reserve University has also announced that the Commonwealth Fund of New York has made appropriations totaling $17,900 for the use of Dr. Wiggers in a three-year program of studies of extracardiac factors of circulation.

Mr. Eli Lilly, Indianapolis, has made a grant of $3,600 for the establishment of a fellowship in protein chemistry, through the committee on the chemistry of proteins of the division of chemistry and chemical technology of the National Research Council.

Competition for Wellcome Medal Announced

The Association of Military Surgeons of the United States announces the annual competition for the Wellcome Medal and prize of $500, established by the late Sir Henry Wellcome for research on subjects helpful to the objects of the Association.

The topic chosen for this year is "Medical and Sanitary Care of the Civilian Population Necessitated by Attacks from Hostile Aircraft." Five copies of the essay must be in the office of the Association in Washington, D. C., by August 20. The medal will be awarded at the annual meeting in Cleveland, October 10–12.

1940 Graduate Fortnight of the New York Academy of Medicine

The 1940 Graduate Fortnight of the New York Academy of Medicine will be held from October 14 to October 25, 1940. The subject of this year's Fortnight is Infections. The purpose of the Fortnight is to make a complete study and authoritative presentation of a subject of outstanding importance in the practice of medicine and surgery.

The Fortnight will present a carefully integrated program which will include morning panel discussions, afternoon clinics and clinical demonstrations at many of

the hospitals of New York City, evening addresses and appropriate exhibits. The evening sessions at the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenograms; pathological and research material; and clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits.

Dr. Mahlon Ashford, F.A.C.P., Executive Secretary of the New York Academy of Medicine, 2 East 103rd St., New York City, will gladly furnish programs upon request.

Radioactive Standards *

A series of radioactive standards are being prepared under the direction of the Committee on Standards of Radioactivity of the National Research Council. These standards will be deposited at the National Bureau of Standards in Washington, D. C., to be issued as working standards to investigators who may desire them.

The standards under preparation at present are:

(1) Radium Standards

(*a*) 100 c.c. solutions sealed in 200 c.c Pyrex flasks containing 10^{-9} and 10^{-11} grams of radium to be used as emanation standards either directly or by subdilution.

(*b*) 5 c.c. solutions sealed in Pyrex ampoules containing 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10, 20, 50 and 100 micrograms of radium to be used as gamma ray standards. If desired, these may be obtained in sets of 13 with two each of the 0.2, 2, and 20 microgram standards.

(2) Thorium Standards

Sealed ampoules containing sublimed $ThCl_4$. These may be used in preparing standard thorium solutions.

Directions for use will be furnished with the standards.

(3) Standard Rock Samples

The following rocks, ground to pass 40-mesh screen and be retained on 100-mesh screen are available in 100 gram samples.

Quartzite (Virginia)
Triassic diabase (Virginia)
Milford granite (Massachusetts)
Chelmsford granite (Massachusetts)
Gabbro-diorite (Massachusetts)
Columbia River Basalt (Idaho)
Berea sandstone (Ohio)
Dunite (North Carolina)
Carthage granite (Missouri)
Carthage limestone (Missouri)
Deccan Trap (India)
Kimberlite (South Africa).

These samples of rock will be analyzed for radium and thorium content and are intended for use as working standards to check methods used in extraction of radon and thoron from rock samples. They may be used for direct fusion in the electric furnace or for carbonate fusion.

All of the above samples will be analyzed at a number of laboratories equipped to make such measurements and ultimately certificates will be issued by the National Bureau of Standards. This work is in progress but will require considerable time for

* This work is being supported in part by a generous grant from the American Philosophical Society to the Massachusetts Institute of Technology.

its completion so that final figures are available only for a part of the samples at the present time.

Accurate knowledge of the radioactive content of the materials of the earth's crust is of primary importance in many phases of geology, geophysics and cosmology. Reliable radioactive standards are also essential in studies of radium and thorium poisoning and in biological and medical investigations using the technique of radioactive indicators, or internal artificial radioactivity therapy. For the latter purposes calibrated standard sources of β-rays will be made available.

It is hoped that the standards which have been prepared by the Committee will provide all workers in these fields with a common basis for comparison of measurements and also improve the accuracy of all measurements of this type. It is likely that they will have other applications and the Committee would appreciate hearing from interested persons who may desire similar standards for their work. The Committee is also glad to coöperate as far as possible in aiding investigators to use these standards to the best advantage and welcomes specific inquiries regarding their use. It is urged that any suggestions regarding other desirable radioactive standards, not at present available, be submitted promptly to the Committee. In particular, it will facilitate the work of the Committee if those laboratories and individuals that can make use of these standards advise the Committee of their probable requirements.

Communications may be addressed to the Chairman, Professor Robley D. Evans, Department of Physics, Massachusetts Institute of Technology, Cambridge, Massachusetts.

L. F. CURTISS,
CLARK GOODMAN,
ALOIS F. KOVARIK,
S. C. LIND,
C. S. PIGGOT,
ROBLEY D. EVANS.

Men engaged in research in medicine, public health, ecology, agriculture, forestry, botany or zoölogy, geography, and other fields, will welcome the announcement that BIOLOGICAL ABSTRACTS is undertaking a more complete abstracting and segregation of the current research literature in bioclimatology and biometeorology. The section *Bioclimatology-Biometeorology* will appear within the section *Ecology* in BIOLOGICAL ABSTRACTS, and will be under the editorship of Mr. Robert G. Stone of the Blue Hill Observatory, Harvard University.

ABSTRACT

MINUTES OF THE BOARD OF REGENTS

Meeting No. 1, March 31, 1940

The first meeting of the Board of Regents, held in connection with the Twenty-fourth Annual Session of the American College of Physicians, occurred March 31, 1940, at the Cleveland Public Auditorium, Cleveland, Ohio, presided over by President O. H. Perry Pepper with eighteen members of the Board present and with Mr. E. R. Loveland acting as Secretary.

Minutes of the preceding meeting and communications were read by the Secretary.

By resolution, a proposal by Dr. Henry H. Lissner, F.A.C.P., that Fellows on reaching the age of sixty-five instead of being placed on the inactive dues-waived list be given the privilege of subscribing $50.00 for active life membership was referred to the Finance Committee for study and report.

By resolution, the Regents directed that the College donate to the medical profession of Madrid, Spain, through the American Union for Nationalist Spain, Volumes XII, XIII and XIV of the "Annals of Internal Medicine."

By resolution, the Editor was directed to publish in the "Annals of Internal Medicine" a summary of the program of the Eighth American Scientific Congress.

The Secretary-General reported the deaths of the following 15 Fellows and 4 Associates since the preceding meeting of the Board of Regents, which brought the total deaths, since the last Annual Session, to 1 Master, 47 Fellows, 15 Associates, or a grand total of 63.

Fellows:

Boardman, Walter Whitney, San Francisco, Calif., February 11, 1940
Browning, Charles Clifton, San Marino, Calif., September 28, 1939
Clayton, John Conover, Freehold, N. J., November 25, 1939
Cowie, David Murray, Ann Arbor, Mich., January 27, 1940
Falconer, William George, Clearfield, Pa., January 3, 1940
Falkowsky, Charles, Jr., Scranton, Pa., December 28, 1939
Hall, Josiah Newhall, Denver, Colo., December 17, 1939
MacCraken, Walter H., Detroit, Mich., March 3, 1940
McCready, Edwin Bosworth, Pittsburgh, Pa., November 3, 1939
Nelson, Albert William, Battle Creek, Mich., January 5, 1940
Osborn, Samuel, Lansing, Mich., December 4, 1939
Ray, Charles Andrew, Charleston, W. Va., January 21, 1940
Riggs, Austen Fox, Stockbridge, Mass., March 6, 1940
Stevens, Martin Luther, Asheville, N. C., January 20, 1940
Van Cott, Joshua Marsden, Brooklyn, N. Y., February 8, 1940

Associates:

Broadwater, Norman Irving, Oakland, Md., February 26, 1940
Cobey, James Carpinter, Frostburg, Md., January 29, 1940
Pumyea, P. Clinton, New York, N. Y., January 18, 1940
Robinson, Frank Hurd, Jr., Hornell, N. Y., November 22, 1939

Dr. Piersol also reported the following additional Life Members since the last meeting of the Board, stating that at previous meetings since the last Annual Session, he had reported five (5) new Life Members, which makes a total for the year of eighteen (18) and a grand total in the College of 134. Of the grand total, twelve (12) are deceased, leaving a balance of 122.

Anthony Bassler, New York, N. Y.
Samuel A. Brown, New York, N. Y.
George B. Crow, Burlington, Iowa
Horace K. Richardson, Stockbridge, Mass.
Thomas F. Duhigg, New York, N. Y.
William S. Kerlin, Shreveport, La.
Charles Thomas Way, Cleveland, Ohio
Edward LeRoy Bortz, Philadelphia, Pa.
Frederick Lane Brown, New Brunswick, N. J.
Walter R. Steiner, Hartford, Conn.
Harry R. Ryan, Rutland, Vt.
Charles Henry Sprague, Boise, Idaho
Lodovico Mancusi-Ungaro, Newark, N. J.

On motion by Dr. Charles H. Cocke, seconded by Dr. James E. Paullin, and regularly carried, the report of the Secretary-General was accepted and filed.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported for that Committee. The Committee had held meetings on February 25, 1940 and March 31, 1940, at which the following candidates were selected for recommendation for election.

On motion by Dr. James E. Paullin, seconded by Dr. Francis G. Blake and regularly carried, it was

RESOLVED, that the following list of 156 candidates for Fellowship shall be and herewith are elected.

(List of elections published in the April Issue of this journal.)

On motion by Dr. James E. Paullin, seconded by Dr. Charles H. Cocke and regularly carried, it was

RESOLVED, that the following list of 144 candidates for Associateship shall be and herewith are elected.

(List of elections published in the April Issue of this journal.)

On recommendation of the Committee on Credentials one Associate was dropped from the Roster because of failure to take up election within one year.

Dr. Sydney R. Miller, continuing his report for the Committee on Credentials, offered the following analysis on the candidates elected to Associateship five years previous, whose maximum five-year term now had terminated:

Advanced to Fellowship	127
Deceased	2
Resigned	4
Failed to qualify and therefore dropped	18
	151 Total

Thereupon, Chairman Miller presented the names of 18 Associates who had failed to fulfill the requirements for advancement and upon resolution regularly adopted these Associates were discontinued on the Roster.

Chairman Miller, continuing his report, nominated Dr. James B. Herrick, F.A.C.P., Chicago, and Dr. William Gerry Morgan, F.A.C.P., Washington, for election to Mastership in consideration of their positions of eminence and their past services to the American College of Physicians. Both nominations were seconded and their elections to Mastership were unanimous.

Chairman Miller also reported that the booklet descriptive of the College and its requirements for membership had been revised and the revision would be presented for review by the Regents later in the week.

President Pepper presented for consideration the presentation of the President's gavel at the time of his induction into office rather than at the end of his term as President. The custom heretofore in the College had been to present the gavel to the retiring President at the end of his term. Dr. Piersol pointed out that the idea of presenting the gavel to the retiring officer is one that is well founded in many societies, the tradition being that it is presented to him by his associates and confreres as a token of their appreciation and as a permanent record of his distinction in office.

After general discussion, Dr. Piersol moved that the present custom be continued; it was seconded and regularly carried that there be no change in this procedure.

Dr. Walter W. Palmer, Chairman of the Committee on "Annals of Internal Medicine" had no report to present. Dr. Maurice C. Pincoffs, Editor of the "Annals," reported that a meeting of the Committee would be held during the week to discuss the question of whether the journal should be extended in size. The journal has been enlarged during the current year in an effort to take up the lag in publication of many articles already accepted. President Pepper mentioned the problem of publishing large reviews, such as the annual rheumatism review, suggesting that the Committee on the Annals should consider this problem from the standpoint of expense and also from the standpoint of the large amount of space occupied to the exclusion of other articles. The rheumatism review has proved extremely popular and valuable.

The Executive Secretary, Mr. Loveland, presented the recommendation of the Executive Offices and of the Editor's Office that the publishing contract for the journal with the Lancaster Press be renewed for another year, from July, 1940, to June, 1941. Both the financial arrangements and service had been highly satisfactory to the College, and the proposal for continuation of the contract was on the same basis as for the preceding year, with no increase or decrease in the basic rates.

On motion by Dr. Pincoffs, seconded by Dr. Charles H. Cocke, and regularly carried, it was

RESOLVED, that the publishing contract with the Lancaster Press for printing the "Annals of Internal Medicine" be renewed for Volume XIV, July, 1940, to June, 1941.

Dr. Hugh J. Morgan, Chairman of the Committee on Postgraduate Education, asked for the approval of the Board of Regents for the printing of an appropriate small certificate of attendance to be given to those members of the College who take the Postgraduate Courses. Dr. Morgan had prepared a sample of the certificate to carry the signature of the President and Secretary-General of the College. Dr. Morgan moved that such a certificate of attendance be authorized, and Dr. Charles H. Cocke seconded the motion.

In the discussion of the motion, it was brought out that this was purely a certificate of attendance and not a certification of the work done; that the certificate should be comparatively small, so that the expense would be slight, and that a record of each certificate should be recorded in the College office; that the certificate should not be of a character recommended for framing, because the College does not want to be in the position of the old proprietary schools, particularly the postgraduate schools; that the certificate should not be spread very broadly, or without any particular control or evidence of accomplishment; that the certificate should not be subject to abuse for advertising purposes. Dr. Morgan again pointed out that it would be purely a certificate of attendance, and that the Postgraduate Courses are very carefully planned and the College is in a position to attest to the excellence of the courses, but not to the degree of efficiency any particular student might attain from attending the course.

Due to the fact that at a later meeting of the Board of Regents the subject of segregating the work of directing the pre-meeting courses to a sub-committee of the Board of Governors from the regular Committee on Postgraduate Education would be considered, action was deferred on the matter of the certificate.

Dr. Roger I. Lee inquired if the motive behind the suggestion for a certificate

was to improve and dignify these Courses and make them more desirable, or if the motive was merely to give a man something that he could show.

Dr. Morgan replied that the motive was to give an incentive and stimulus to men in the College to take the courses, and that the recognition of their taking the courses would add dignity; also that it might encourage the men who are giving the courses to put them on an ever increasingly high plane.

Dr. Morgan, continuing the report of his Committee: "The College Committee on Postgraduate Education wishes to report on the meeting of the Advisory Council on Medical Education, February 10 at Chicago, where the College was represented by Dr. James H. Means and Dr. Hugh J. Morgan. The Advisory Council on Medical Education adopted the following resolutions:

"'(1) Inasmuch as the internship is now universally regarded as a part of the basic preparation for the practice of medicine and to be fully satisfactory must be integrated with the medical course proper, the Advisory Council on Medical Education recommends that the Association of American Medical Colleges in coöperation with national medical and hospital organizations and the Federation of State Medical Boards and state licensing bodies, and after consultation with the Council on Medical Education and Hospitals of the American Medical Association, should formulate minimum educational standards for the internship and should prepare a list of hospitals in this country which meet these standards.'

"Through the insistence of members of the College, the phrase 'after discussion with the Council on Medical Education and Hospitals of the American Medical Association' was inserted in the resolution and the resolution was passed.

"I personally was not sure that the Association of American Medical Colleges was wise in making any such survey, but it wanted to do so because it felt it could render service to its students. It did seem important that we recognize the work that has been going on for many years, that has been done by the Council on Medical Education and Hospitals of the American Medical Association. That point was recognized by the Committee as a whole and was incorporated in the resolution.

"Your Committee points out that Dr. Morris Fishbein in the current issue of the Journal of the American Medical Association, devoted to medical education, has vigorously attacked the action of the Association of American Medical Colleges in their decision to go into the matter of evaluating internships. The second resolution adopted by the Advisory Council on Medical Education was as follows:

"'(2) Inasmuch as the internship is now universally regarded as a part of the basic preparation for the practice of medicine, the Advisory Council on Medical Education recommends to the Federation of State Medical Boards that an internship of not less than twelve months and of satisfactory educational content be required for admission to the state licensing board examinations in all states.'

"This report is made simply as a matter of information to the Regents."

The Board of Regents took no action on the above part of Dr. Morgan's report, whereupon Dr. Morgan continued: "Your Committee also wishes to report to the Regents now on a meeting of the Joint Conference Committee of the American Board of Internal Medicine, the American College of Physicians and the Council on Medical Education and Hospitals of the American Medical Association, held in Chicago, February 4, as an organization meeting. The Committee agreed that (1) a coöperative plan is now in force among these three organizations; (2) in general, procedure already adopted by the Council on Medical Education and Hospitals would be continued in the evaluation of residencies and fellowships in Medicine; (3) the Conference Committee will assist in the formulation of standards that will express more accurately the requirements for graduate training in Medicine; (4) when feasible, members of the American Board of Internal Medicine, or of the Committee of the

American College of Physicians, will accompany the Council's examiners to some of the hospitals under consideration in order to participate in the inspection; (5) application blanks and inspection reports will be submitted to the American College of Physicians and the American Board as promptly as possible after the completion of the survey; and, finally, a joint approval of this material will be made either by correspondence or conference, and the result of the Committee's decision relative to it will be transmitted to the Council on Medical Education and Hospitals of the American Medical Association.

"The Committee on Postgraduate Education also wishes to report that five Postgraduate Courses have been given preceding the Annual Session. Course No. 1, 'General Medicine,' under Dr. Cyrus C. Sturgis at the University of Michigan Medical School, was attended by 18 Fellows and 15 Associates; total, 33; Course No. 2, 'Medicine in Industry,' under Dr. Frank J. Sladen at the Henry Ford Hospital, Detroit, was attended by 3 Fellows and 2 Associates and 2 candidates for membership, and 31 non-members (23 of these non-members were registered directly by Dr. Sladen); total, 38; Course No. 3, 'Allergy,' under Dr. Robert A. Cooke, at the Roosevelt Hospital, New York City, was attended by 2 Fellows and 6 Associates; total, 8. This course was limited to 8, and many applicants had to be turned away; Course No. 4, 'Postgraduate Survey of the Hematologic Diseases,' under Dr. Charles A. Doan at the Ohio State University College of Medicine, Columbus, was attended by 22 Fellows and 15 Associates, and 1 non-member; total, 38; Course No. 5, 'Cardiovascular Diseases,' under Dr. Fred M. Smith at the State University of Iowa College of Medicine, was attended by 16 Fellows and 11 Associates; total, 27. There was a grand total of 144 students, 110 of whom were members (61 Fellows and 49 Associates) of the College. They were drawn from 33 States and from Canada."

On motion by Dr. Morgan, seconded by Dr. William D. Stroud, and unanimously carried, it was

RESOLVED, that a letter of thanks, conveying sincere appreciation of the Board of Regents for the effort and time devoted to giving these Courses, be sent to each of the five Directors of the 1940 Postgraduate Courses of the College.

At this juncture, Dr. Morgan continued his report: "I want to bring before the Regents the following matters: (1) the desirability of passing on to the Board of Governors the continuation study program initiated by the College in 1938, which has been under the direction of the Regents' Committee since that time. The Courses have become established as a definite part of the College's educational program. I personally feel that since the Governors have expressed keen interest in this aspect of the College work and since they are in closer touch with members who attend these Courses probably the responsibility of arranging and organizing the Courses should be passed on to them. (2) The Conference Committee of the Council on Medical Education and Hospitals of the American Medical Association has come into being, and the College thus has an opportunity to participate in the definition of standards for medical internships, assistant residencies and residencies, to help in a survey of institutions for such residencies, and to guide the Council of the American Medical Association in its evaluation of these residencies. I should like to recommend that the Regents delegate the responsibility for the annual Postgraduate Courses and the Conference Committee work to a committee of the Governors. Both of these points are matters that ought to be gone into after due consideration, and I do not ask for any action. In fact, I think it might be well to defer action until a subsequent meeting of the Regents, after they have had adequate time to consider the matter."

President Pepper pointed out that the work of the Committee on Postgraduate Education of the College had proved a very arduous task, and that the Chairman has been called upon for tremendous amount of work and travel. Dr. Pepper expressed the hope that the Regents would continue to control the policy of the College in relation to graduate education, and that he thought it would be a mistake to take the entire

matter out of the Regents' hands, whereas it would be quite practical to delegate the direction of the Postgraduate Courses to a committee of the Governors and thus lessen the duties of the Regents' Committee.

Dr. Pepper also expressed the opinion that the pre-meeting Postgraduate Courses ought to be correlated in some way with the sectional or regional meetings, and that the Board of Governors should be asked to create a committee to take charge of these Courses, but that the Regents should continue their Committee, perhaps as one of educational policy, and that Dr. Morgan, if possible, should be persuaded to continue as Chairman.

Dr. Morgan then asked for the Regents' consideration of the establishment of a different kind of fellowship, namely, in addition to its Research Fellowships, it should establish fellowships in Clinical Medicine, to the end that a man who has had an internship, or an assistant residency, but who has failed to get a third or fourth year as resident may have an opportunity to continue his institutional work. There are not enough residencies to go around for the number of men who are asking for them, Dr. Morgan contended, and he felt that a modification of the College's present Research Fellowship, or, perhaps, an extension of it, to include clinical fellowships would be very gratefully received by many men who hope to qualify for the American Board of Internal Medicine certification and later for admission to the College.

In the general discussion that followed, Dr. Cocke pointed out that inasmuch as this would entail a large financial obligation on the part of the College, the Finance Committee would have to be consulted, and that action should be taken only after due consideration at a full meeting.

President Pepper pointed out that there were three points in the report of the Committee on Postgraduate Education which will come up for later discussion: (1) the giving of some form of certificate of attendance for those completing the Postgraduate Courses, this certificate to be in a simple form which would discourage its use in an undesirable way and would merely state that the College and the Credentials Committee had taken cognizance of the fact that the student had pursued the course; (2) the matter of delegating to the Board of Governors certain responsibilities for the conduct of the Postgraduate Courses; (3) the establishment of fellowships in Clinical Medicine.

On motion put and seconded and regularly carried, it was

RESOLVED, that the report of the Committee on Postgraduate Education be received and filed.

Due to the unavoidable absence of Dr. James Alex. Miller, Chairman, the report of the Committee on Finance was made by Dr. Roger I. Lee:

"The Finance Committee held a meeting this morning with the Treasurer and went over the College accounts, budgets and other data. The Committee is happy to report that the finances of the College are in excellent condition, with a surplus of income over expenditures for the current year. The Finance Committee recommends the transfer of $25,000.00, or more, from the General Fund to the Endowment Fund, with the hope of building up the Endowment Fund to some substantial figure, so that it may produce an income which will be of great value to the College. The Finance Committee recommends that this be done in these so-called profitable years against the possibility of lean years. The Finance Committee would point out that the income from investments has continued at about 4 per cent, which it regards very favorable. There was a capital loss of about $5,000.00 in securities sold, which, however, is somewhat counteracted by the fact that there has been an improvement in the market value of securities still held. One item that gave the Finance Committee concern was the fact that in 1936 the percentage of bonds was about 85 per cent of total holdings, but gradually there has been a reduction in the percentage of bonds, partly on account of the depreciation of some of these bonds and the appreciation of

stocks, so that now the percentage of bonds is under 50 per cent. The stocks that the College owns are mainly preferred stocks, and the percentage of common stocks is still very low, about 10 per cent, in general terms. It is the decision of the Finance Committee, unless otherwise directed by the Board of Regents, to develop the percentage of bonds, in order to restore that percentage to a considerably higher figure than at the present time."

On motion by Dr. George Morris Piersol, seconded by Dr. Walter W. Palmer, and unanimously carried, it was

RESOLVED, that $25,000.00 shall be transferred from the General Fund to the Endowment Fund as of this date.

President Pepper pointed out that the Finance Committee had been following the advice all along of its investment counsellor, the Girard Trust Company.

Dr. Lee stated that the Finance Committee had not in the present instance voted to approve some of the suggestions of the investment counsellor, in regard to the purchase of more stocks, but had approved their recommendations for the purchase of bonds.

On motion by Dr. Robert A. Cooke, seconded by Dr. Charles H. Cocke, and unanimously carried, it was

RESOLVED, that the report of the Finance Committee be approved and filed.

On motion by Dr. James E. Paullin, seconded by Dr. Sydney R. Miller, and regularly carried, it was

RESOLVED, that an appropriation of $134.38 be made to cover the traveling expenses of Drs. Hugh J. Morgan and James D. Bruce, College representatives on the Conference Committee on Postgraduate Training in the field of Internal Medicine, to the Chicago Conference, February 4 and February 11–13.

President Pepper then called for a report of the Committee on Survey and Future Policy.

In the absence of Dr. James Alex. Miller, Chairman, Dr. Maurice C. Pincoffs reported that the Committee had held a very brief meeting with three members present and with no report other than one of progress to make. Certain matters which had come up at the preceding meeting of the Committee at Philadelphia in December, 1939, were discussed. One of these was the use of educational films, or the possible rôle of the College in connection with educational films. The Chairman, Dr. James Alex. Miller, had contacted the Film Center of New York City and obtained certain sample films for showing at the end of the First General Session of the Cleveland meeting. The Film Center was reported to be a source of information as to what it might cost the College if it instead of mobilizing films now extant and loaning them out were to make films of its own for distribution to its regional meetings, or for such other educational purposes. The Film Center had estimated that a short film would cost from $2,500.00 to $3,500.00, and another organization reported that the cost would be $3,000.00 and upward. The impression of the Committee on Future Policy and Survey was that such figures wouldn't compare well with university experience in making films, and that no program could be based on such figures without further investigation.

Dr. Pincoffs stated that there had been further discussion of the feasibility of publishing in the "Annals of Internal Medicine," from month to month, announcements that relate to available educational opportunities in Internal Medicine. The Committee felt that if such notices were restricted to those of universities and of comparable bodies, such as the New York Academy of Medicine, it would offer no great difficulty to the Executive Secretary's office and the Editor's office to publish these, and they might be of considerable utility to the members who are looking at certain times of the year for postgraduate courses. The Committee felt that it would be better policy not to include the more general meetings, which are not strictly in the field of Internal Medicine.

President Pepper referred to the fact that Dr. James Alex. Miller had contributed a chapter to the College History, and that said chapter was in the hands of Dr. Pincoffs and available for any of the Regents to read. In the latter part of the chapter, Dr. Miller had discussed the present plans and future hopes of the Survey Committee.

Continuing, Dr. Pepper said that the Committee on Scientific Exhibits had been for some reason instructed to report through the Committee on Future Policy and Survey, but asked the Chairman, Dr. Francis G. Blake, for any report he might have available.

Dr. Blake reported briefly of progress. The Committee had been collecting a certain amount of information concerning the holding of scientific exhibits, and another meeting of the Committee will soon be held, when more definite recommendations will be presented.

On motion by Dr. D. Sclater Lewis, seconded by Dr. Roger I. Lee, and regularly carried, the report of the Committee on Future Policy and Survey and Dr. Blake's report were received and filed.

(Many members of the Regents and Governors, as well as some members of the College viewed the films referred to, as shown in the public meeting room on Monday, April 1, and the general consensus of opinion was that this activity would not justify the necessary expenditures; in other words, that the College could utilize its funds in other directions to the greater advantage of its members.)

At the request of President Pepper, Mr. Loveland, as secretary, reported that the Historian, Dr. William Gerry Morgan, had sent a message to the effect that it had been impossible to have the College History published and presented at this time, due to several contributions not yet being completed. The Regents furthermore had instructed Dr. Morgan to cover the first twenty-five years in the College History, which would include the current Cleveland Session.

President Pepper announced that the terms of Dr. Jonathan C. Meakins and Dr. G. Gill Richards, as appointees from the American College of Physicians on the American Board of Internal Medicine, will expire June 30, 1940, and that appointments would be in order.

On motion by Dr. Robert A. Cooke, seconded by Dr. Roger I. Lee, and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians shall reappoint as its representatives on the American Board of Internal Medicine for the term July 1, 1940 to June 30, 1943, Dr. Jonathan C. Meakins, of Montreal, and Dr. G. Gill Richards, of Salt Lake City.

After the reading of announcements concerning coming events, meetings, etc., in connection with the Twenty-fourth Annual Session, the meeting adjourned.

Attest: E. R. LOVELAND,
Executive Secretary

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OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore, Md.

Executive Office—4200 Pine Street, Philadelphia, Pa.

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. DOE, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

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